ACUTE ON CHRONIC LIVER FAILURE - CLINICAL PROFILE, PRECIPITATING FACTORS, OUTCOME AND PREDICTORS OF MORTALITY

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CERTIFICATE

This is to certify that the dissertation entitled "ACUTE ON CHRONIC LIVER FAILURE-CLINICAL PROFILE, PRECIPITATING FACTORS, OUTCOME AND PREDICTORS OF MORTALITY" is a bonafide work done by Dr.HEMAMALA.V S at Madras Medical College, Chennai in partial fulfilment of the university rules and regulations for award of D.M., Degree in Medical Gastroenterology (Branch-IV) under my guidance and supervision during the academic year 2010 -2013.

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I solemnly declare that this dissertation entitled "ACUTE ON CHRONIC LIVER FAILURE-CLINICAL PROFILE, PRECIPITATING FACTORS, OUTCOME AND PREDICTORS OF MORTALITY"was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2010-2013 under the guidance and supervision ofProf. MOHAMMED ALI M.D, D.M. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of D.M. Degree in Medical Gastroenterology (Branch-IV).

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TABLE OF CONTENTS

INTRODUCTION

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Liver failure can develop acutely in a patient with no preexisting liver disease (acute liver failure) or as an acute decompensation of a chronic liver disease. Recently it has been noted that a subgroup of patients develops acute deterioration in previously compensated cirrhosis and are considered to have acute on chronic liver failure (ACLF). This deterioration is secondary to an acute event and multi organ failure leading to increased mortality at three months. In contrast to chronic liver disease these patients have a rapid downhill course with the development of multiorgan failure and high short term mortality. One important concept in this group of patients is the potential reversibility. The term reversibility does not mean that underlying chronic liver damage is reversible, but rather the acute deterioration of the liver function due to the precipitating event is reversible. The pathophysiological basis ACLF was initially described by Jalan et al [1]. There is no clear cut definition of ACLF in the western literature. Asia Pacific association of study of liver (APASL) has defined it as acute hepatic insult manifested by jaundice and coagulopathy complicated within four weeks by ascites or encephalopathy [2]. The cause for acute deterioration can vary from infectious causes like sepsis, viral hepatitis and non hepatotrophic viruses' infection or noninfectious causes like alcohol, drugs, gastrointestinal bleeding, toxins and surgery. There is controversy

regarding whether sepsis can precipitate ACLF or it is the result of ACLF. Though numerous studies have been published in western literature on cirrhotic patients admitted to ICU, most of them have not differentiated organ failure as part of progressive worsening in end stage cirrhosis from acute on chronic liver failure [10, 15, 17, and 18]. There are very few studies from India in this subject. H Garg et al have recently published a prospective study on ACLF patients [9]. Etiology of chronic liver disease and the acute precipitants differ between various geographical locations. AS ACLF carries a high mortality it is essential to identify prognostic factors. In general it has been noted that score evaluating the severity of disease like APACHE and SOFA score are better than liver specific score like Child Pugh score[18.20,21]. Management of ACLF requires good intensive care to prevent the development of organ failure or to support the failing organs. Use of various extracorporeal liver support systems have been studied in various studies[14,25-28].Even though there is an improvement in biochemical parameters and in hepatic encephalopathy ,there is no significant survival benefit. Liver transplantation is the only curative treatment [29].

This prospective study aims to look at the clinical profile, precipitating factors, outcome prognostic factors in ACLF admitted in a tertiary care hospital.

AIM OF THE STUDY

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The aims of the study are as follows

1. To study the clinical profile of patients with acute on chronic liver failure
2. To study the underlying chronic aetiology and acute precipitants
3. To study the 30 day and 90 day mortality
4. To study the various predictors of mortality

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Cirrhosis occurs due to a wide spectrum of hepatocellular insults and it is rarely reversible. Once initiated, it progresses from a compensated state to decompensated state resulting in morbidity and mortality. These complications are the direct result of the impaired liver function that is due to a decreased functional capacity of the hepatocyte mass and the architectural distortion that impairs normal hepatic blood flow. Liver transplantation is the only curative treatment.

Recently a subgroup of patients with chronic liver disease has been identified who have acute downhill course in a previously compensated liver disease due to an acute insult. This clinical entity has been termed as acute on chronic liver failure (ACLF). It is characterized by rapidly developing liver failure due to an identifiable precipitating event leading to increased short term mortality due to multi organ failure. There is an element of reversibility when identified early.

Definition

Asia pacific Association of study of liver diseases (APASL) consensus guidelines and the working definition by EASL-AASLD on ACLF is given in table 1[2, 3]

Table 1 Definition of ACLF
Asia pacific Association of study of liver diseases (APASL) consensus guidelines
Acute hepatic insult manifesting as jaundice (serum Bilurubin = 5 mg/dL)and coagulopathy(INR = 1.5 or prothrombin activity <40%), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.
Working definition by EASL-AASLD on ACLF
Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure

End stage vs. acute on chronic liver failure

Cirrhosis is the last phase of a progressive parenchymal cell damage leading to nodular parenchymal regeneration and progressive fibrosis. Liver insufficiency occurs due to progressive hepatocyte loss .When the hepatocytes reach below a critical functional liver cell mass liver failure sets in (figure 1).

There is a substantial overlap between the clinical presentation of end stage and acute on chronic liver failure .These include jaundice, hepatic encephalopathy or

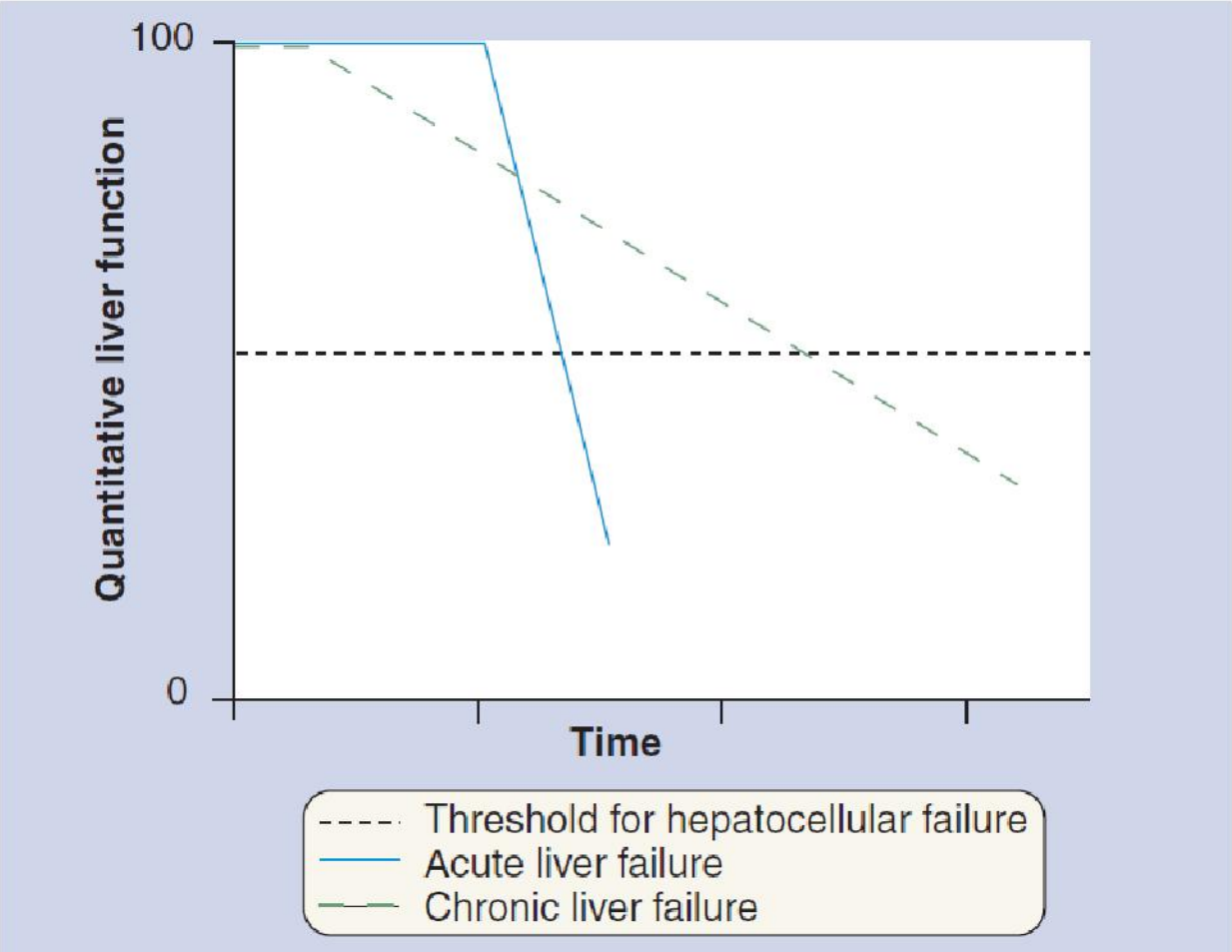

Figure 1. The 'critical mass' concept. Liver failure results from the surpassing of a critical threshold of hepatocellular function, either acutely (acute liver failure) or due to progressive chronic liver disease (chronic liver failure).

Hepatorenal syndrome. But ACLF is characterized the element of reversibility and an acute precipitating event in most of them. In addition most patients

progress towards multi organ failure and have high short term mortality. So ACLF refers to acute deterioration of liver function by a precipitating event which is subsequently followed by other organ failure whereas 'end stage liver disease' refers to a chronically decompensated state due to progressive deterioration of the underlying liver disease.

ACLF must also be differentiated from acute or fulminant liver failure which occurs in patients without any evidence of preexisting liver disease. Cerebral edema is a prominent feature of acute liver failure. AASLD defines acute liver failure as the presence of coagulopathy and encephalopathy in patient with no preexisting liver disease with disease duration of less than 26 weeks.

Why this interest in ACLF?

Increasing interest in ACLF in recent years is due to two reasons. First is the Consideration of Model for End-stage Liver Disease-(MELD) score (based on serum bilirubin, serum creatinine and International normal ratio) for allotting organs in liver transplantation. This score predicts the 3 month mortality. Before the implementation of MELD donor organs were allotted on the basis of waiting time. But after the implementation of MELD sickest patients get priority, so ACLF patients get an opportunity to receive an organ based on severity of the disease.

Second reason for the increasing interest is the potential for reversibility and the need for use of liver support devices. In end stage liver disease only liver transplant can cure the patient. In ACLF management of acute precipitating event (e.g. anti-viral in Hepatitis B activation) can bring the patient back to previous critical liver cell mass. Additionally use of liver support devices can be considered to give time for the liver to recover or as bridge to transplantation.

Reversibility

Reversibility is the main component of ACLF [43, 44]. The term 'reversibility' here does not mean that cirrhosis is reversible, but rather that there is a component of acute deterioration that is reversible. Jalan et al have studied a large group of cirrhotic patients hospitalized for various complications [5]. They noted a mortality of 53% which indicates that reversibility in half the patients. What is not known is the degree to which reversibility can occur. Reversibility does not mean just survival, but rather return to baseline function.

Precipitating event

This is the second important component of ACLF.There is an identifiable precipitating event in ACLF. This is in contrast to end stage liver disease where there is continued hepatocellular damage leading to worsening of disease. This

new ‘acute’ insult may or may not be related to original etiology of the underlying chronic liver disease. But experts agree that the acute precipitating event should be of hepatic origin [2]. For example it could alcoholic hepatitis on a preexisting alcoholic liver disease or super added acute viral hepatitis E in alcoholic liver disease. The reversibility depends on the severity and nature of acute insult and degree of underlying chronic liver disease.

These acute precipitating events can be infectious or noninfectious (Figure2 and table 2). There is a difference between the west and the east in the major etiological agents. Viral infections are more common in the east whereas alcohol and drugs are more common in the west [15, 18-20].

Among infectious causes reactivation hepatitis B virus infection is one of the major cause of ACLF. This reactivation can be spontaneous or due to immunosuppression, cancer chemotherapy or immune restoration due.to highly active antiretroviral therapy. Another important infectious cause of reactivation is acute hepatitis E. Prevalence of acute hepatitis E in ACLF varies from 13-21% [6, 7].various bacterial,spirochetal and fungal infections can also affect the liver.

Among the noninfectious causes alcoholic hepatitis is a common cause of acute deterioration. Other causes include drug induced liver injury and intake of native or herbal medications.

Sepsis is an important component of ACLF and its outcome. Most western studies have included sepsis as a precipitating event. But this is controversial and it has

Infectious etiology	Non-infectious etiology
Hepatotropic and non-hepatotropic viruses Reactivation of hepatitis B (overt or occult) or hepatitis C Other infectious agents afflicting the liver	Alcohol: active drinking within 4 weeks Hepatotoxic drugs, herbs Flare of autoimmune hepatitis or Wilson's disease Variceal bleed Surgery Unknown hepatotoxic etiology

Table 2 Precipitating events in ACLF

been argued that sepsis can worsen the condition, but by itself it cannot directly cause a hepatic insult. APASL guidelines have not included sepsis as an acute precipitant.

Acute variceal bleeding is one of the features of decompensation in the natural history of cirrhosis. Variceal bleeding has been included as one the acute precipitants of ACLF in some western studies. Variceal bleed is an expression of elevated portal pressure and is not due to an acute insult. However no consensus has been reached in APASL regarding including variceal bleed as an acute insult.

Major surgical procedures can also lead to acute deterioration in a patient with cirrhosis. However there is a conflicting opinion among experts about including surgery as an acute insult or not. According to APASL guidelines surgery can be include as an acute insult if the clinical syndrome otherwise fits the current definition.

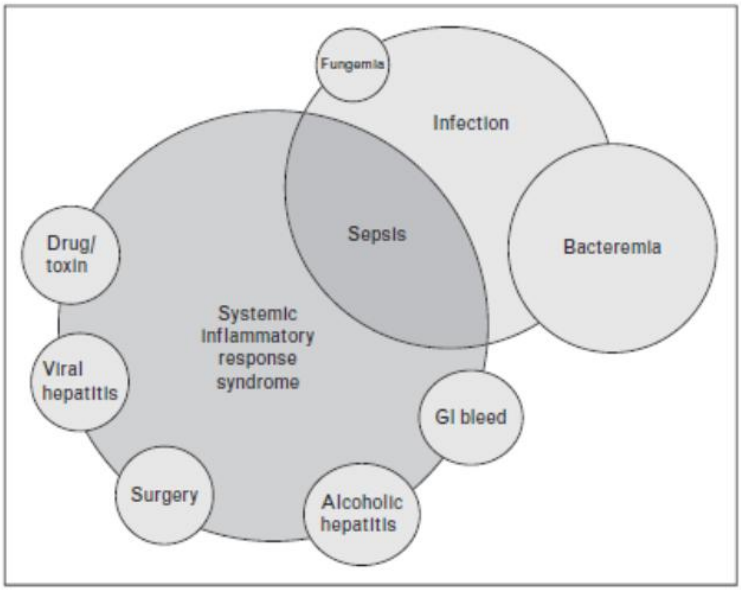

Figure 2 Precipitating events in ACLF

In some patients in spite of best evaluation acute precipitant may not be found.

Hitendra Garg et al have done large prospective study on ACLF patients. In their study hepatitis B was the most frequent cause of underlying disease. Alcohol was the second common cause. Etiology of underlying disease was not known in about a quarter of patients. Common acute precipitant was Hepatitis

B reactivation in underlying chronic hepatitis B (85%) and super added alcoholic hepatitis (81%) in alcoholic liver disease. In 14% of them had hepatitis E was identified as acute precipitant.

In a retrospective study by Duseja et al alcohol was the most common etiology(61%) followed by cryptogenic (14%) and other causes which include hepatitis B ,hepatitis c, autoimmune, and Wilson disease[41].

ROLE OF SEPSIS

Sepsis is an important component ACLF. There is controversy regarding including sepsis as an acute precipitant in ACLF.APASL guidelines does not include sepsis as an acute event. How can sepsis precipitate liver failure? It has been suggested that lipopolysaccharide (LPS) found in bacteria produces liver injury by inducing apoptosis and also by ischemic injury due to accompanying circulatory disturbances. The apoptotic effect of LPS is augmented by the release of Tumor necrosis factor (TNF) [1]. However it has been argued that sepsis alone cannot directly cause liver injury, but can worsen the condition of the patient.

Microorganism-associated molecular patterns (MAMPs)-induced proinflammatory response leads to widespread inflammation, multi organ

failure, and death [45]. Organ failure is due to tissue hypo perfusion and hypoxia. Hypo perfusion is due to decreased perfusion pressure and flow, micro thrombi formation, reduced red blood cell deformability, blood mal distribution, and tissue edema caused by increased capillary permeability. In addition, cells may be unable to properly utilize available oxygen due to impairment in mitochondrial respiration in part due to nitric oxide (NO) overproduction. Finally, cellular infiltrates, in particular neutrophils, damage tissue directly by releasing lysosome enzymes and superoxide-derived free radicals.

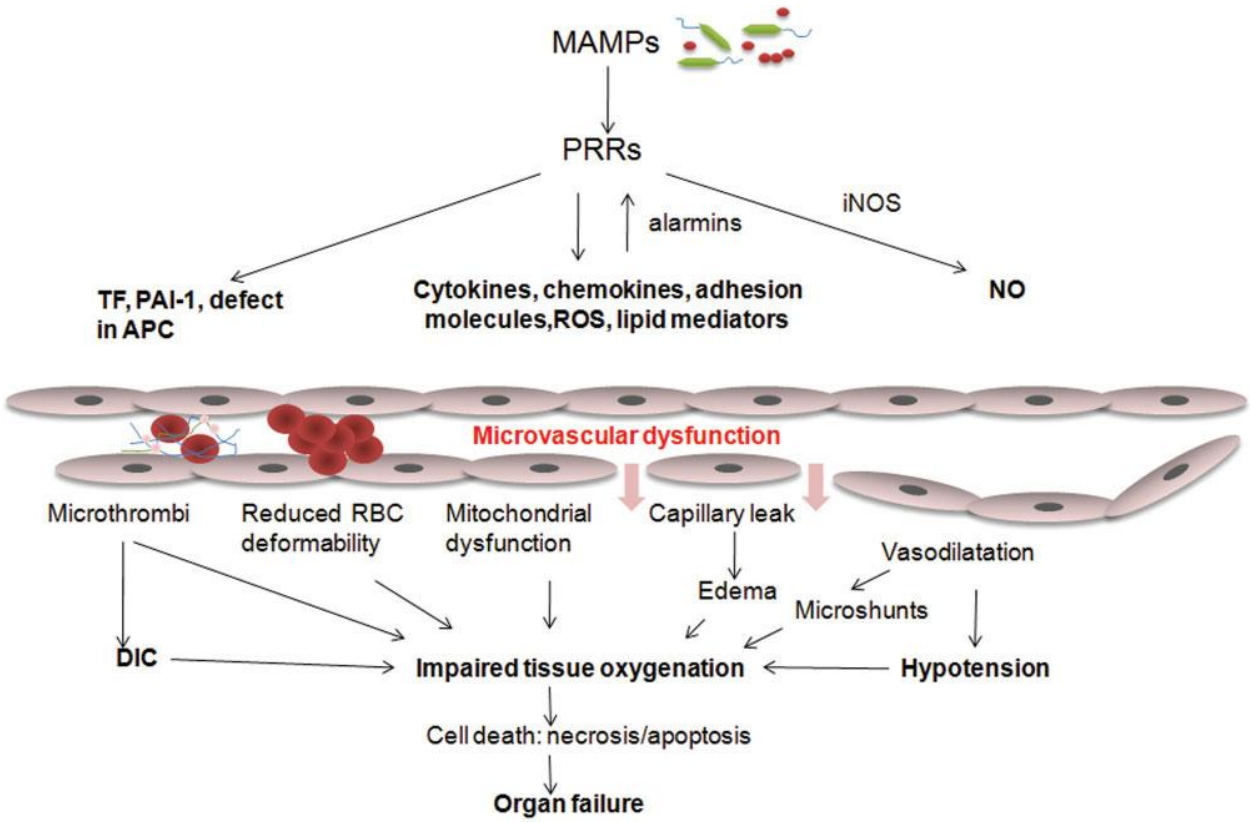

Figure 3-Mechanism for sepsis induced liver failure; MAMPs-Microorganism-associated molecular patterns,PRRs-pattern recognition receptors

PATHOPHYSIOLOGY

The main pathophysiological mechanisms involved in ACLF are the presence of Systemic Inflammatory Response syndrome (SIRS), release of cytokines, neutrophil dysfunction and altered nitric oxide levels. What tilts the balance from well compensated state to ACLF is the deregulated inflammation due to altered host response to injury. The 'Toxin hypothesis' was considered to be

main mechanism leading to organ failure in ACLF (Figure 4). The Toxin hypothesis suggests there is accumulation of toxins due to impaired hepatic detoxification and metabolism.The toxins are usually albumin like aromatic amino acids, mercaptans, ammonia, and nitric oxide [8].

Although toxin accumulation is an important factor, at present pathophysiology of ACLF is considered to be much more complex. Bacterial translocation (BT) also plays an important role in its pathogenesis. Bacterial translocation occurs due to increases intestinal permeability and is frequently seen in cirrhotics. In 30-50% of patients with cirrhosis infection is the cause for admission [9].How ever bacterial translocation alone is not enough to explain the organ dysfunction. It has to be accompanied by abnormal immune response and vascular hyperreactivity due to inflammatory cytokines(figure 5).The degree of BT is related to degree of underlying liver disease than to the portal hypertension(PHT) itself. This is evidenced by increasing prevalence of BT with increasing CTP scores[30].

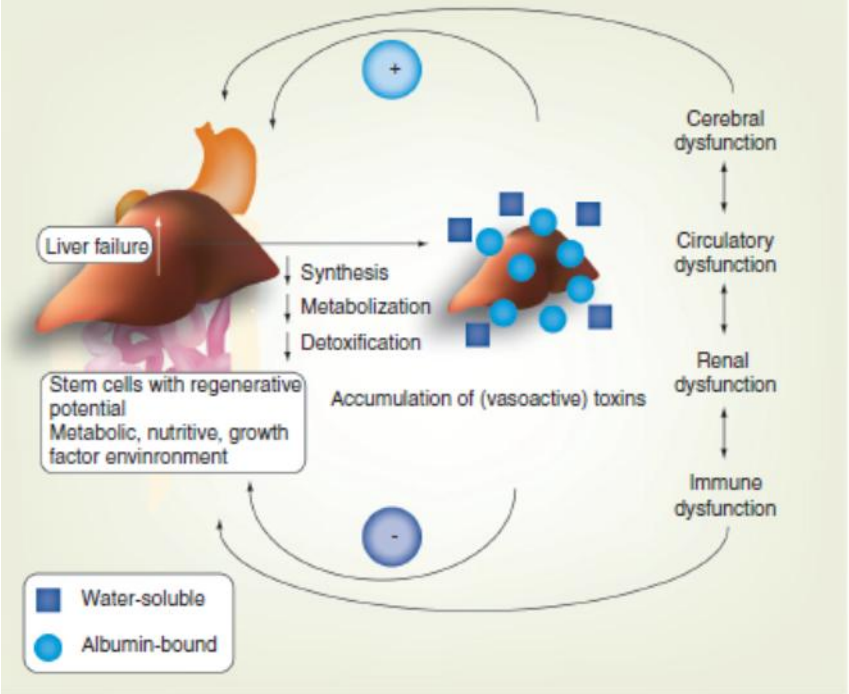

Figure 4. The toxin hypothesis: the failing liver results in the accumulation of a variety of toxins, which are presumed causative of end-organ dysfunction. The combined actions of accumulated toxins and end-organ dysfunction further aggravate liver injury and incapacitate the regenerative environment.

Mechanisms of immune dysfunction in ACLF

Immune dysfunction or immune paralysis is a significant component in cirrhosis [38]. Decreased synthetic function of liver leads to decreased opsonisation capacity (figure 6). Opsonisation is important for bacterial phagocytosis. Another important cause of immune dysfunction is the portal hypertension. Kuppfer cell is a component of reticulo endothelial system (RES). Because of the shunting of blood in collaterals the bacteria evade the RES and enter systemic circulation [10]. Phagocytic activity of mononuclear cells and neutrophils are impaired. There is

Increased production of TNF α which means that immune system though dysfunctional is in a persistently activated state. Activated kuppfer cells produce huge amount of cytokines, chemokines and oxygen derived free radicals (figure 7). These include interleukin (IL)-1, IL-17, IL-18, and TNF α [32].

Presence of bacteria and their toxins leads to activation of inflammatory cascade and the sepsis syndrome. This inflammatory cascade is responsible for the features of SIRS. The hyper dynamic circulation of cirrhosis is further aggravated by this unbalanced immune response .So perfusion to vital organs is affected. Ischemia aggravates the organ injury kidneys and brain and finally multi organ failure and death is produced.

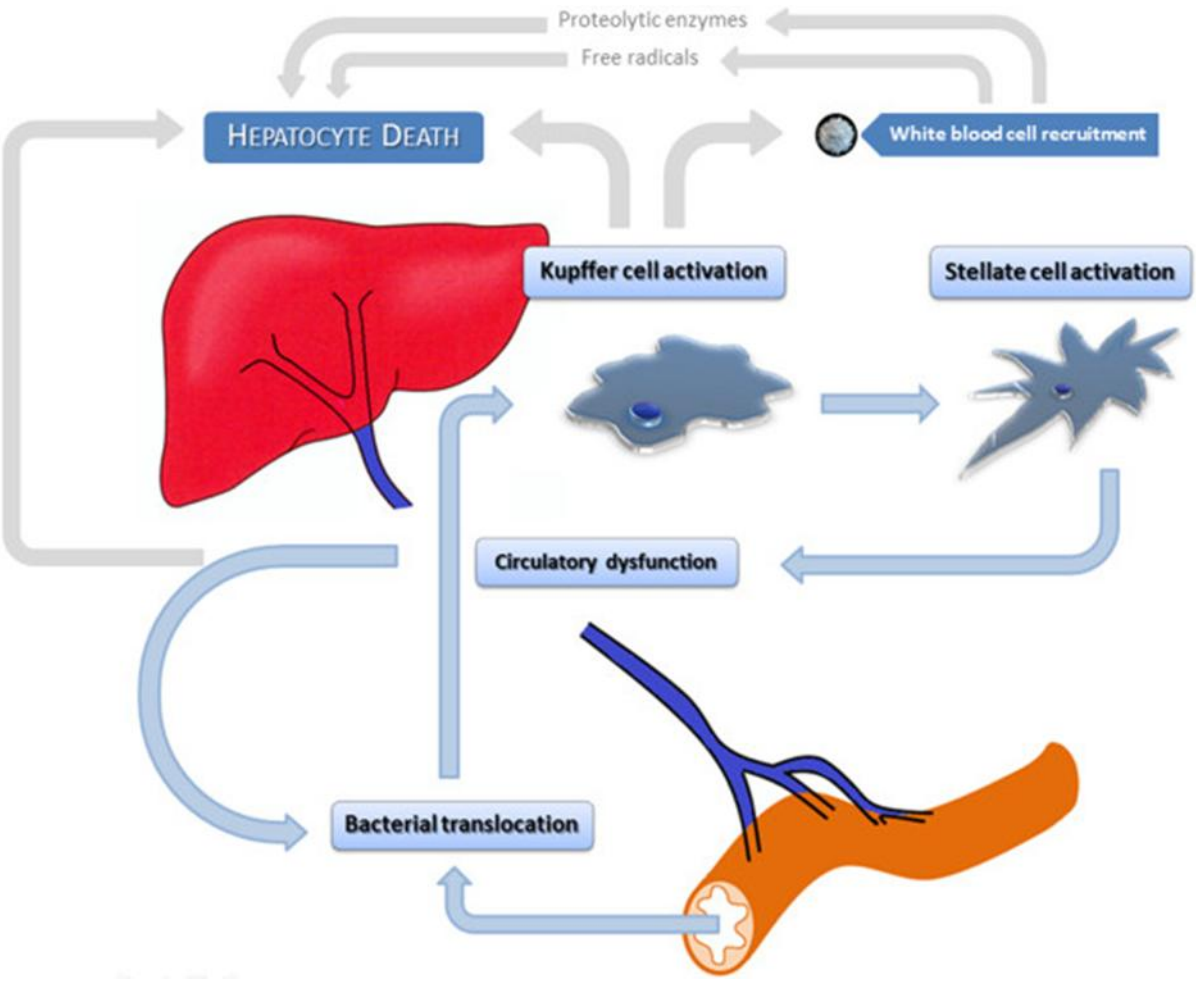

Figure 5 Role of Bacterial Translocation in ACLF

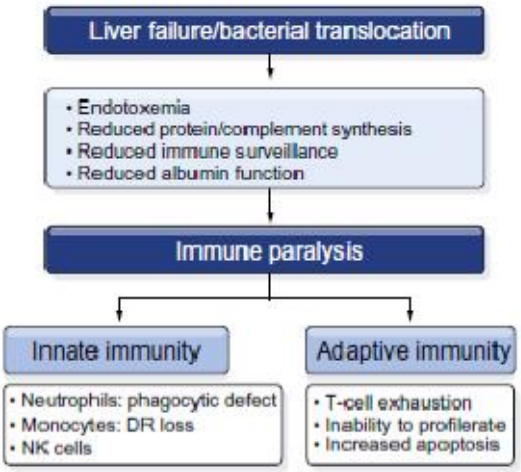

Figure 6 Immune dysfunction of ACLF

Clinical implications of immune dysfunction

The main implication of immune dysfunction in ACLF is that infection is common in them. This has been demonstrated in various studies as follows: Infection is a cause for hospital admission in 15-35% of cirrhotics in contrast to 5-10% in general population. Secondly various therapeutic interventions has been tried to modify this immune response. Corticosteroids and pentoxyfylline, an inhibitor of TNF α have been used in severe acute alcoholic hepatitis

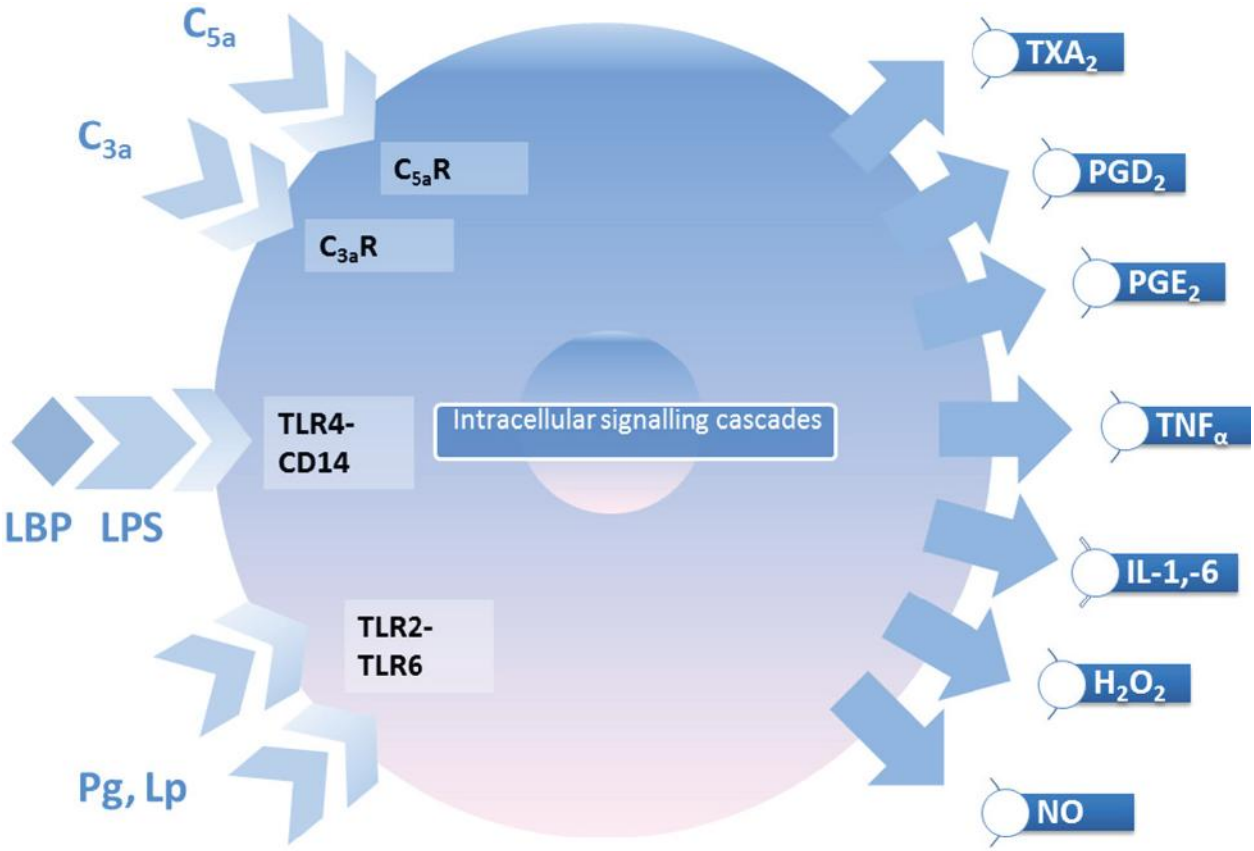

Figure 7 Role of Activated Kuppfer cells in ACLF

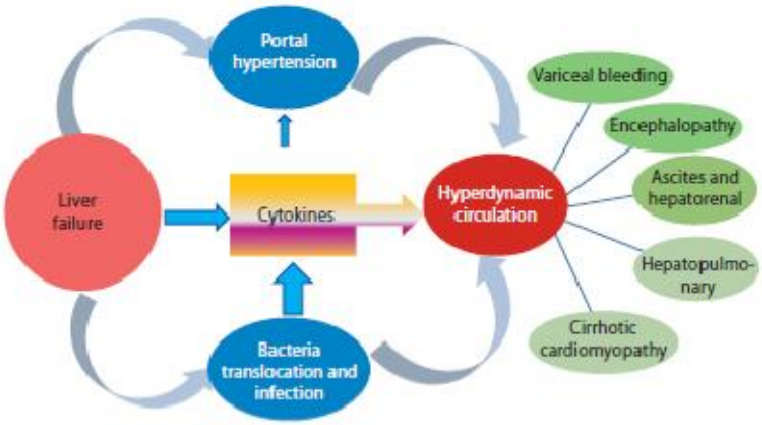

Figure 8 Role of cytokines in ACLF

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PIRO concept in ACLF

A concept similar to PIRO (Predisposition, Injury, Response and Organ failure) concept in sepsis has been proposed in ACLF.Predisposition is indicated by the severity of the underlying illness. Injury is indicated by the nature and severity of the precipitating event. Response is defined by host response to injury, which determines the severity of inflammation and risk of infection. Organs indicate the extent of organ failure. Categorizing the patients into these entities helps us to define the interventions and prognosis at different levels.

NATURAL HISTORY AND PROGNOSIS

There is limited data on natural history of cirrhosis progressing to organ failure and its outcome. In a study by Jalan et al. 497 cirrhotic patients admitted with acute deterioration mortality was 8% in those without organ failure whereas it was 53% in those with organ failure [5]. Increasing number of organ failures is associated with worse prognosis. Time from organ failure to death was 10(1-40) days. Mortality was higher (78%) in those with recent decompensation in previous 6 months than in those without (34%).Changes in SOFA scores improved sensitivity and specificity in predicting mortality. Irrespective of the precipitant presence of SIRS significantly predicted mortality. There have been

very few prospective studies which have looked into the natural history of ACLF. Most of the studies that have been published vary in their inclusion criteria as different definitions of ACLF are used in west and east.

Many prognostic factors that determine the outcome in ACLF have been studied. In general scoring systems pertaining to severity of liver disease such asChild-Pugh score or Model of End Stage Liver Disease (MELD) do less well than the scoring systems used in critically ill patients like the Sequential Organ Failure Assessment SOFA) or the Acute Physiology, Age and Chronic Health Evaluation (APACHE)scores. In fact once organ failure has begun mortality is determined by the severity of the organ failure and not by the severity of the liver disease [17-21].

Katoonizadeh et al in their prospective study on early features acute on chronic liver failure in alcoholic liver disease compared patients with ACLF with chronic decompensated cirrhosis [12]. They found an in-hospital mortality of 46% in ACLF in contrast to an in-hospital mortality of 10% in chronic decompensated cirrhosis. Early signs of infection, positive systemic inflammatory response syndrome at admission and ductal stasis of bilirubin were early markers of ACLF. This was the first prospective cohort study attempting to characterize acute on chronic liver failure.

In the study by H Garg et al 29% had organ failure at admission [9]. By one week 46% had developed organ failure. Number of organ failure correlated with hospital mortality-it was 26% in those with only one organ failure and >90% in those with four or more organ failures. The 30 day and 90 day mortality was 50% and 63% respectively. Presence of hepatic encephalopathy, high WBC count, low platelets, low serum sodium, high serum creatinine, large varices and high HVPG were found to be associated with mortality. But on multivariate analysis only hepatic encephalopathy, low serum sodium and high INR were found to be predictors of mortality.MELD, SOFA and APACHE-II, had better predictability than CTP in predicting mortality.

In the systemic review published by Wlodzimirow et al in Liver International, they have done tried to identify various prognostic markers from all the studies published on ACLF[25].They have concluded that there is underlying differences between various studies making comparison difficult. Age, hepatic encephalopathy, model for end-stage liver disease score, total bilirubin and International normalized ratio (prothrombintime) are considered to promising markers for future evaluation.

European Consortium on Chronic Liver Failure (CLIF) has done large multi centric prospective observational study (CANONIC) on Acute on Chronic liver failure [13]. The main aim of this study is to define the natural history of ACLF

and evaluate the prevalence, precipitating mechanisms, and risk factors for its development, survival and the risk factors of mortality. Preliminary data was presented in the International liver congress in 2012 and has reported a mortality of 35.5% in contrast to only 4.5% in those without ACLF. It was significantly associated with bacterial infections and active alcoholism. No precipitating cause was found in about 20 %.Four grades of ACLF were identified by them

- ACLF-1: renal failure or a non-renal organ failure associated with creatinine 1.5-2 mg/dL and/or grade I-II encephalopathy
- ACLF-2: 2 organ failures
- ACLF-3: 3 organ failures
- ACLF-4: 4-6 organ failures

This would be one the largest prospective studies on ACLF and would help us to better define and prognosticate the disease.

MANAGEMENT OF ACLF

The key point in the management of ACLF in contrast to the management of chronic end stage liver disease is the identification of the precipitating event and prevention and management of multi organ failure. Organ failure is seen

as part of gradual deterioration in end stage liver disease and only curative option is liver transplantation. However in ACLF if the liver damage due to the acute precipitant is reversible prognosis is better. Due consideration should be given to prevention of infections and organ dysfunction. This can be done by judicious use of antibiotics, fluid, albumin and vasopressors.

Spontaneous reactivation of chronic hepatitis b is a common cause of ACLF. Short term mortality ranges from 30-40% [33-35].liver transplantation is curable but it is inaccessible to most. Antivirals have tried. Tenofovir is a potent nucleotide analog which has been used in chronic hepatitis B. In a study byGarg etal 27 patients of ACLF were randomized to receive tenofoviror placebo [36]. Tenofovir has improved the mortality from 15%to57%. Among the survivors there is not only a significant decline in HBVDNA levels but also an improvement in severity scores like CTP and MELD. More than two log reduction in HBVDNA levels within two weeks was associated with better survival.

Ribavirin has been tried for acute hepatitis E in ACLF in small number of patients. In a study from AIIMS,Delhi [37] four patients with genotype 1 acute HEV in ACLF were treated with 200-600mg/day ribavirin for 3-24 weeks (median 12 weeks).All the patients had survived and had cleared the virus by 3-8 weeks.

Another novel therapy that has been used in ACLF is granulocyte colony stimulating factor (G-CSF). It was initially used by Di Campilli et al [39] and it was shown to induce stem cell mobilization. Ina randomized study by Garg et al 47 patients of ACLF were randomized to receive 5ug/kg G-CSF or placebo in addition to standard medical treatment[40]. Survival was 66%in the treatment group and 26% in the placebo group. Improvement in severity scores was better in the treatment group. Also the number of complications like hepatorenal syndrome, hepatic encephalopathy and sepsis was lower. It acts by mobilization of CD34 stem cells from bone marrow.

Role of liver transplantation

The recent increasing interest in ACLF is due to the use of MELD for organ allocation. With the use of MELD sickest patients get priority and hence many of the patients with ACLF can get transplanted. There are very few studies on liver transplantation in ACLF. Albert Chan et al [30] have described their series of 149 patients who underwent liver transplantation for ACLF. Two third of them were due to chronic hepatitis B. Their 5 year survival was more than 90%, similar to the results obtained by other indications. Indications for liver

transplant is based on the prognostic scores which suggest death within the next three months[2].Patients who are hemodynamically unstable and are on large dose of vasopressors, severe infections and cerebral edema or intracranial bleeding are not candidates for liver transplant.

Role of liver support devices in ACLF

Artificial liver support devices play an important role in supporting the liver till it recovers or as a bridge to liver transplantation. Molecular adsorbent recirculating system (MARS) has been studied widely. In MARS, blood is dialyzed across

An albumin-impermeable membrane with a molecular weight cut-off of 50 to 60 kDa against 20% human serum albumin, which is continuously stripped by subsequent passage through columns of charcoal and an anion exchange resin. Water-soluble substances are removed by a low-flux dialyzer connected to the secondary circuit. Prometheus separates the patient's own albumin/plasma by a membrane with a molecular weight cut-off of 300 kDa and directly passes it over two columns containing different adsorbents. Water-soluble substances are cleared by a high-flux dialyzer directly inserted into the blood circuit.

In RELIEF trial conducted in Spain patients with ACLF were randomized to MARS or to standard medical therapy [14]. MARS had an acceptable safety profile, decrease in creatinine and bilirubin. The most consistent benefit has been seen with improvement of hepatic encephalopathy. It is efficient in removing cytokines. However no survival benefit could be demonstrated. Role of MARS as a bridge to transplantation still needs to be defined. So at present it is not routinely used in the treatment of ACLF.

MATERIALS AND METHODS

This prospective study was conducted in Department of Medical gastroenterology, Rajiv Gandhi Government General Hospital, Chennai. The study period was from November 2011 to February 2013. Consecutive patients of acute on chronic liver failure were enrolled.

Inclusion criteria

Consecutive patients with ACLF as defined by APASL guidelines in Table 1 were included- Patients complicated by ascites and encephalopathy within four weeks of onset of jaundice (bilirubin >5 mg/dl) and coagulopathy (INR >1.5) .These patients can have either previously diagnosed or undiagnosed compensated chronic liver disease. Patients are considered to have chronic liver disease by the presence of any of the following –nodular contracted liver on ultrasound, portal vein ≥13 mm, and oesophageal varices ≥2 on endoscopy or fibrosis ≥ 2 on histology [9].

Exclusion criteria

1. Hepatocellular carcinoma
2. Portal vein thrombosis
3. Patients with any disseminated malignancy
4. HIV

5. Pregnant women
6. Age less than 18 years or more than 80 years

Data collection

Data was collected prospectively on patient's demographics, clinical features, laboratory parameters, disease severity, aetiology of the underlying chronic disease and the acute insult, presence of multi organ dysfunction and outcome.

Clinical profile and course

Once a diagnosis of ACLF has been made data was collected prospectively on patient demographics, clinical symptoms and signs, laboratory parameters, complications and outcomes. Extensive history was taken from the patients and the attending relatives. This included history of alcohol intake, other drugs including native medications, abdominal distension, fever, altered sensorium, upper gastrointestinal bleed and risk factors for viral hepatitis.

All patients underwent detailed physical examination and vital signs were recorded. Presence of spiderneavi, gynaecomastia, hepatomegaly, ascites, abdominal wall collaterals and grade of encephalopathy was noted. Hepatic encephalopathy was graded according to West Haven system into grade 0 to 4.

Blood was collected for complete blood count, urea, creatinine, electrolytes, liver function tests, prothrombin time, INR, C - reactive protein and viral markers. All the parameters were repeated every 1-3 days depending on the severity of the illness. Ascitic fluid analysis was done for Serum ascitic fluid albumin gradient, cell count and culture. Spontaneous bacterial peritonitis was defined by the presence of > 250 neutrophils per mm^3 or positive ascitic fluid cultures .Blood cultures were sent in all patients and other body fluids were sent for cultures when clinically indicated.

All patients under went USG abdomen and PV Doppler study and following details were recorded- Liver span, surface nodularity of liver, Size of the spleen, size of portal and splenic veins; presence of portal-systemic collaterals, presence of ascites .

Upper gastrointestinal endoscopy was done to document the grade of varices. Esophageal varices were classified according to grading system by Paquet as given in table. Presence of gastric varices and portal hypertensive gastropathy were noted.

Grade 0	No varices
Grade I	Varices, disappearing with insufflation
Grade II	Larger, clearly visible, usually straight varices, not disappearing with insufflation
Grade III	More prominent varices, locally coil-shaped and partly occupying the lumen
Grade IV	Tortuous, sometimes grape-like varices occupying the esophageal lumen

Table 3 Paquet Classification of oesophageal varices

In HBs Ag positive patients samples were sent for HBV DNA levels, HB e Ag, Anti HBc IgM and total. In Patients positive for HCV samples were sent for HCV RNA levels and genotype. Patients positive for anti HEV IgM were considered to having acute hepatitis E.

Assessment of severity and organ dysfunction

Following severity scores were calculated for all patients-Child –Turcotte-Pugh (CTP), MELD and modified SOFA score (Table 5 and 6). MELD score is calculated as follows -logarithmic equation (0.957 × log [creatinine mg/dl] + 0.378 × log [bilirubin mg/dl] + 1.120 × log [international normalized ratio] + 0.643) Presence or absence of Systemic Inflammatory response syndrome (SIRS) was noted (Table 4). Maddrey's Discriminant function (MDF) was calculated in patients who had alcoholic liver disease as follows: [4.6 ×

(patient's prothrombin time – control prothrombin time, in seconds)] + serum bilirubin level, in milligrams per deciliter. These scores were calculated at baseline and also repeated at weekly intervals. Organ failure was defined by the presence of SOFA score of 3 or more for the respective organ system. Presence of two or more extra hepatic organ failure is defined as multiorgan failure.

Evidence of a systemic response to infection defined by the presence of two or more of the following signs
1. Fever (temperature >38.3°C) or hypothermia (rectal temperature < 35.6°C) 2. Tachycardia (heart rate of >90 beats/min) 3. Tachypnea (respiratory rate >20 breaths/min or PaCO2 <32 mm Hg) or need for invasive mechanical ventilation 4. Alteration of the white cell count >12,000 cells/mm3,<4,000 cells/mm3 or >10% immature neutrophils (bands)

Table 4 SIRS (Systemic Inflammatory Response Syndrome) criteria

Criteria	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate	Large or refractory to diuretics
Bilirubin (mg/dl)	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
Prothrombin time (Seconds prolonged)	<4	4-6	>6
Class A 5-6 points, Class B 7-9 points, Class C 10-15 points			

Table 5 Child-Pugh-classification

SOFA SCORE	0	1	2	3	4
RESPIRATION					
Pa_{O_2}/F_{IO_2} (mm Hg)	>400	≤400	≤300	≤200	≤100
pulse oximeter oxygen saturation (SpO2)*	SpO2 >90% at room air	SpO2 ≤90% at room air, increased above 90% with FiO2 0.24 (1 l/min nasal O2)	SpO2 ≤90% at room air, increased above 90% with FiO2 0.30 (mask)	SpO2 ≤90% at room air, increased above 90% with FiO2 0.50 (mask)	SpO2 ≤90% at room air and despite FiO2 0.50 (mask)
COAGULATION					
Platelets × $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
LIVER					
Bilirubin (mg/dl)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
CARDIOVASCULAR					
Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
CENTRAL NERVOUS SYSTEM					
Glasgow Coma Score	15	13–14	10–12	6–9	<6
RENAL					
Creatinine					
mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
(µmol/L) or urine output	(<110)	(110–170)	(171–299)	(300–440) or <500 mL/day	(>440) or <200 mL/day
Respiratory failure is defined by a SOFA score ≥3 or requirement for mechanical ventilation; hematologic failure by a score of 4 and/or INR >2.5; liver failure by a score of 4; cardiovascular failure by a score ≥2;neurologic failure by a West Haven score ≥3 or requirement for endotracheal intubation to prevent aspiration pneumonia; renal failure by a score ≥2 or requirement for renal-replacement therapy.					

Table 6 Modified SOFA (Sequential Organ Failure score score)

Statistical analysis

All the data were entered on a excel sheet. Mean and median were calculated for appropriate variables. All the variables between survivors and non-survivors or transplanted patients were compared. Variables significant by univariate analysis were again compared by multivariate analysis. P value less than 0.05 was taken as significant. Statistical analysis was done by SPSS 16 software.

RESULTS

RESULTS

During the study period, 57 patients presenting with clinical picture suggestive of acute on chronic liver failure were screened. Of these 12 patients were excluded due to following reasons –presence of hepatocellular carcinoma (3),portal vein thrombosis (2),patients left against medical advice (5) and no evidence of chronic liver disease(2).So totally 45 patients were enrolled for the study. There were forty two males and three females (male: female 14:1).The mean age of presentation is 42 years (range18-70 years) (figure 9,10 & Table.7).

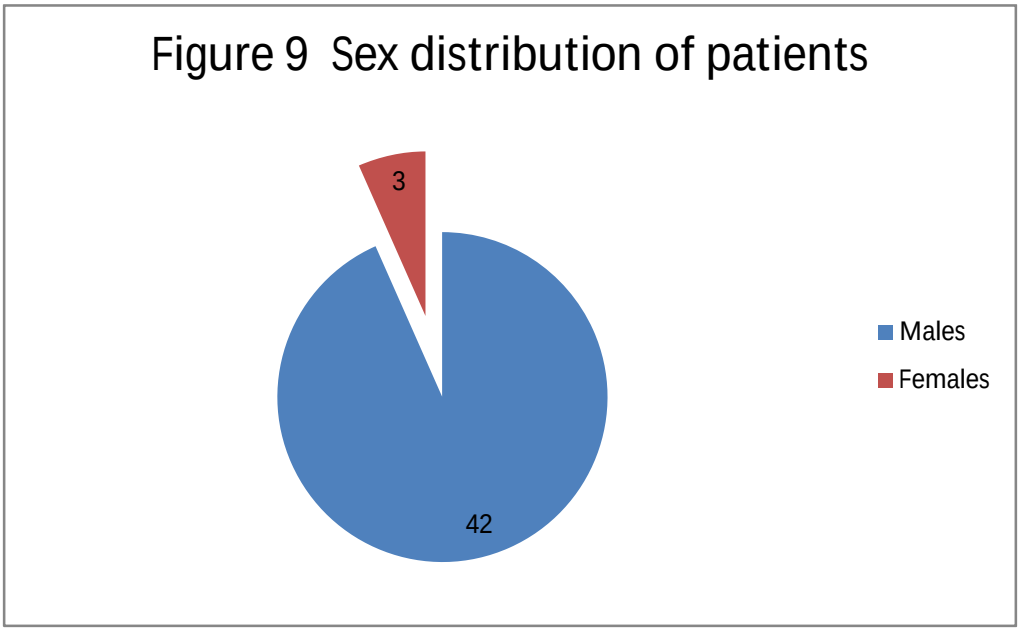


Table.7: Age distribution		
Age in years	No. of cases	Percent
≤ 20	2	4.4
21 - 30	5	10.8
31 - 40	11	24.4
41 - 50	15	33.3
51 - 60	10	22.2
61 - 70	2	4.4
Total	45	100.0

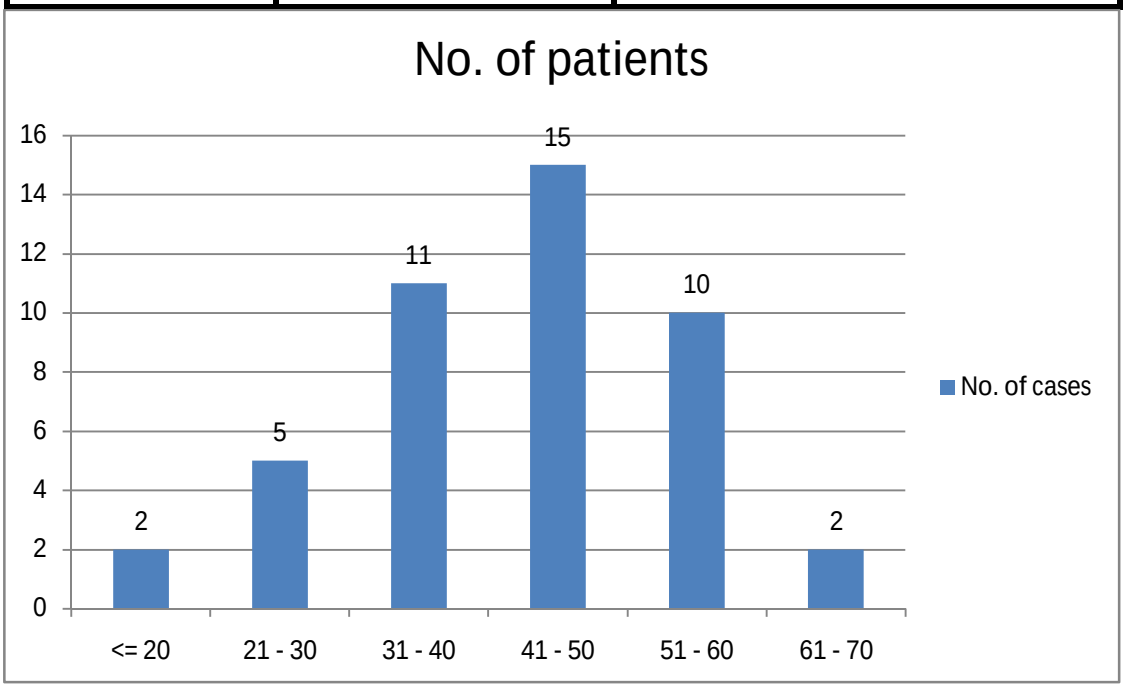


Figure 10 Age distribution of patients

Clinical features and laboratory findings

Acute onset of jaundice with ascites was seen in all the patients. Most patients had severe jaundice with a median of 15.8 mg/dl (range5.28-38).Encephalopathy was seen in 18 (40%) patients at admission. During the hospital stay another 12 patients (total 30 patients i.e. 66% developed encephalopathy). Out of this 30, 12 patients had grade 2 encephalopathy and 9 patients had grade 3 or more encephalopathy (Table 10 and figure 11).

13 patients (28.9%) had history of gastrointestinal bleeding in the form of hematemesis or melena. 5 of these patients developed bleeding in the form of melena after admission and it was probably related to the coagulopathy.Endoscopy was done in most patients (41).It was not done in the rest of them because of hemodynamic instability. Most (28 patients -62 %)) had grade 2 or more esophageal varices.27 (60%) patients had portal hypertensive gastropathy

13 (28.9%) patients had hepatomegaly and 28 (62.2 %) had splenomegaly.2 of the patients had spider neavi and 2 had parotid enlargement.

The median hemoglobin was 9 gm./dl (range 4.3-13).The median platelets were 102000/cu mm(8000-321000).Median AST and ALT values were 137 and

118 IU/L .Median albumin values were low 2.9gm/dl(1.8- 3.9). INR was prolonged (median 1.94, Range 1.5-4.5). INR was more than 2.5 in 11 patients (24%).

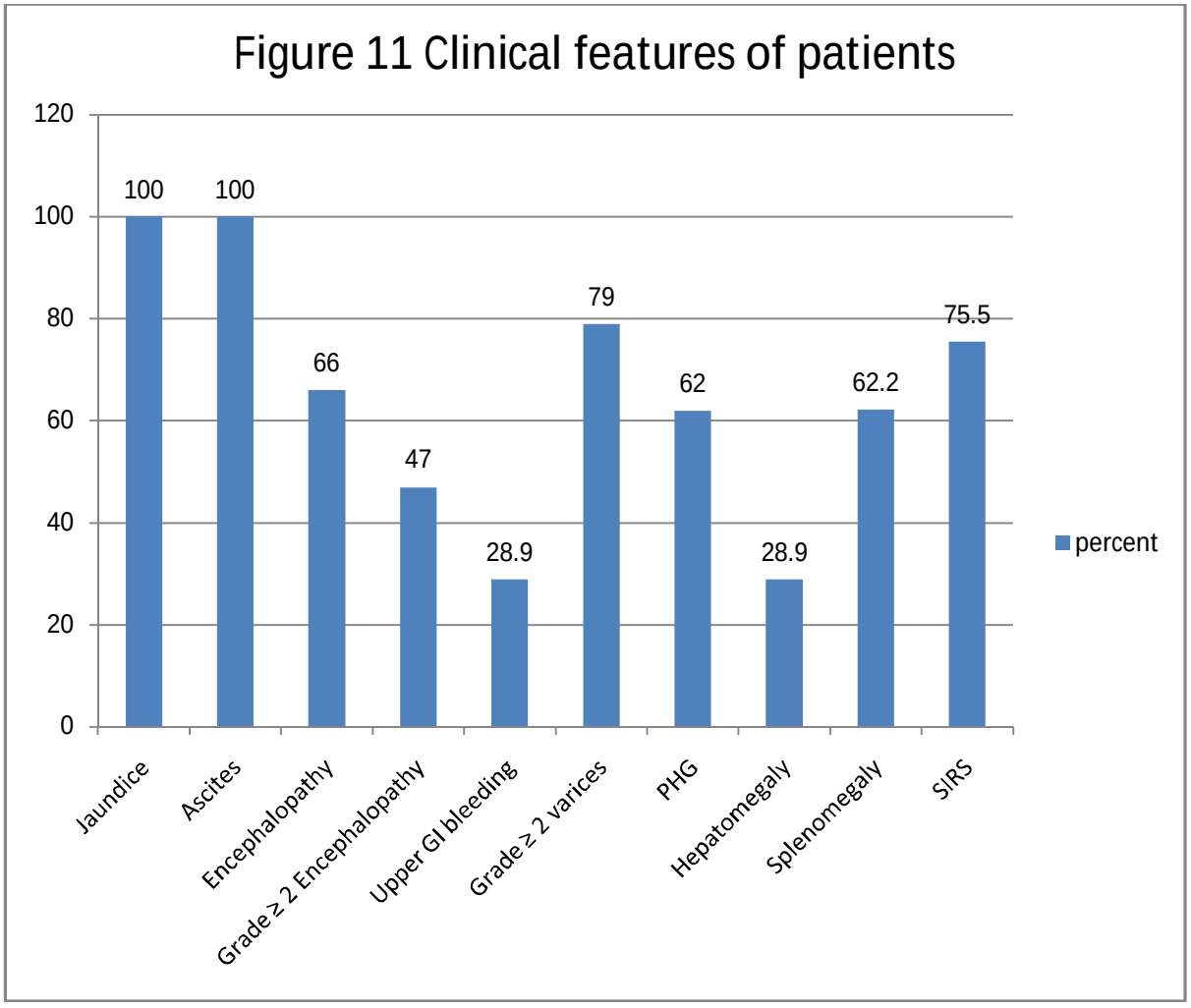


Table 10 Baseline clinical features of 45 patients

Clinical feature	Number	Percentage
Median Age (years)	42	19-70
Males	42	93
Jaundice	45	100
Ascites	45	100
Mean duration of symptoms(days)	21	Range (7-28)
Encephalopathy	30	66
Grade ≥2 encephalopathy	21	47
Upper GI bleeding	13	28.9
Grade 2 or more esophageal varices	28	79%
Portal hypertensive gastropathy	27	62
Hepatomegaly	13	28.9
Splenomegaly	28	62.2
Spidernaevi	2	4.4
Parotid enlargement	2	4.4
Presence of SIRS	34	75.5

Table 11: Baseline Laboratory findings of all the patients

Parameter	Median	Range
WBC(cells/cu mm)	14400	580-26200
HB (gm./dl)	9	4.30-13
Platelets (cell/cu mm)	102000	8000-321000
RBS(mg/dl)	98	40-266
Urea(mg/dl)	38	12-199
Creatinine (mg/dl)	.95	0.60-4.5
Sodium(meq/L)	134	115-145
K+(meq/L)	3.90	2.30-5.9
Bilirubin(mg/dl)	15.70	5.28-39
AST(IU/dl)	137	45-350
ALT(IU/dl)	118	24-1642
Proteins(g/dl)	5.60	3.60-6.6
albumin(g/dl)	2.90	1.8-3.9
PT(sec)	23.90	17.0-45
INR	1.94	1.50-4.5
CRP(mg/dl)	48	6-238
MDF	67.30	40.2-128
MELD	26	18-40
SOFA	6	3-14
CTP	12	9-14

Infection in ACLF

23 patients (51%) had history of fever. Most patients had elevated WBC count with a median of 14400 (range 580-26200) cells/mm^3. (Figure 12& 13)However infection could be documented in only in 14 (31%) patients. 5(11.1%) patients had spontaneous bacterial peritonitis .Blood cultures were positive in 3 patients, ascitic fluid cultures in 3 and urine culture in 2 patients . Klebsiella is the most common organism isolated followed by pseudomonas and E.coli. Other foci of infection include pneumonia (2), cellulitis (2) and peri anal abscess (1).All these patients had signs of sepsis at admission except one. One patient developed pneumonia after admission. Apart from this, one patient had parvovirus induced aplastic anemia. Among the patients with documented sepsis 6 patients survived and 7 died. All patients had elevated CRP except 4 (9%).Median values was 24 mg/dl (range 6-238)

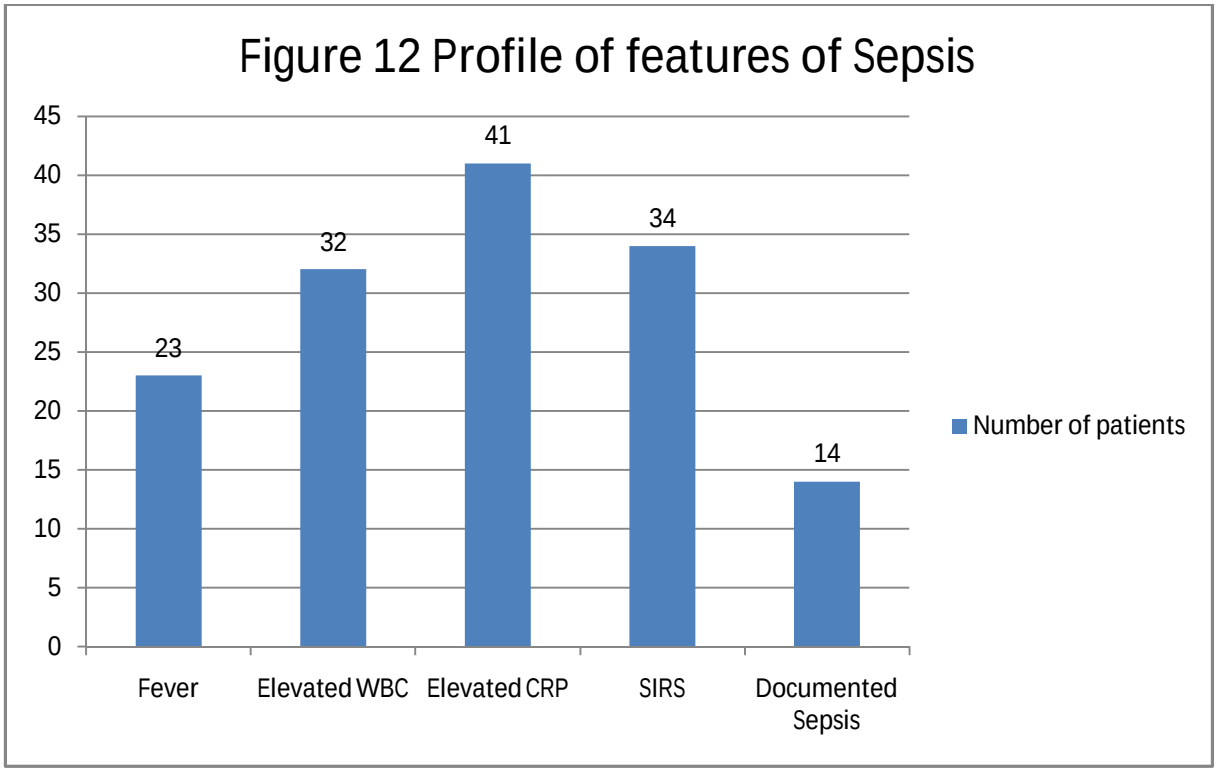


Figure 12 Profile of features of Sepsis
45
40
35
30
25
20
15
10
5
0
23
32
41
34
14
Fever
Elevated WBC
Elevated CRP
SIRS
Documented Sepsis
Number of patients

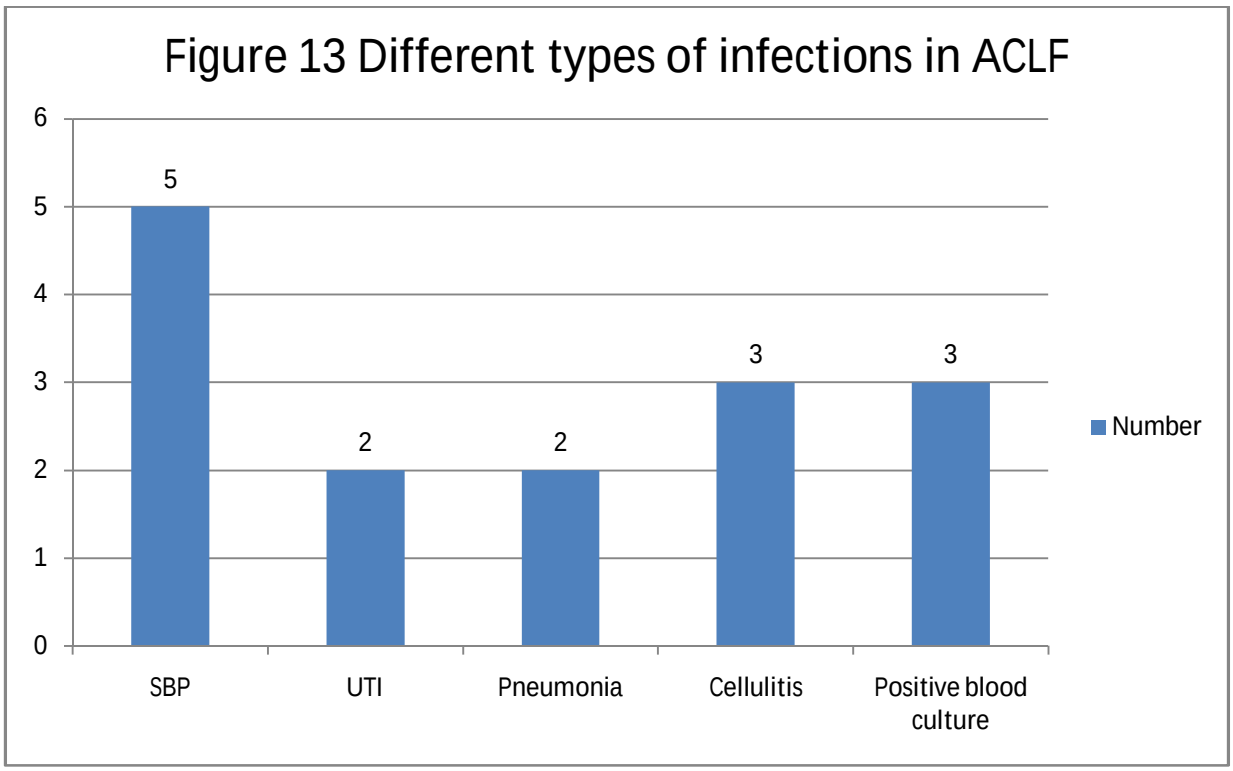


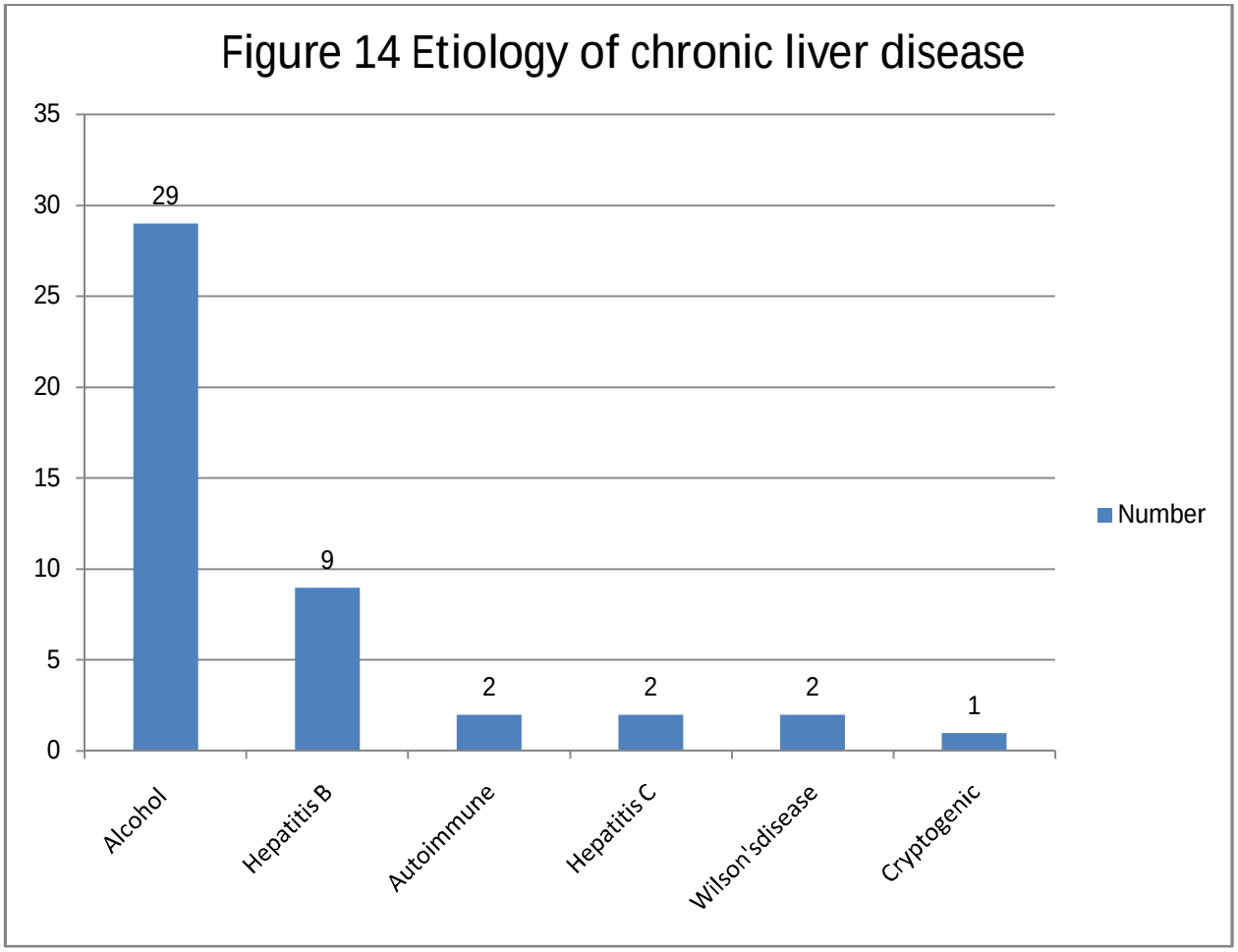
Figure 13 Different types of infections in ACLF
6
5
4
3
2
1
0
5
2
2
3
3
SBP
UTI
Pneumonia
Cellulitis
Positive blood culture
Number

Aetiology of liver disease

Aetiology of chronic liver disease and reasons for acute exacerbation was evaluated. Most common cause of underlying liver disease is alcoholic liver disease (64.5%) followed by hepatitis B (20%). (Table.12 & Figure.14) Among the alcoholic liver disease super added alcoholic hepatitis is the most common (82%) cause followed by acute hepatitis E (4.4%). Most patients were actively drinking alcohol almost till few days before admission. Among patients with chronic hepatitis B, reactivation of hepatitis B is the most common cause followed by hepatitis E and alcohol. There were two patients with autoimmune liver disease and two patients with hepatitis C in who cause for acute deterioration could not be found. In two patients with Wilsons disease cause for acute deterioration was due to drug induced liver disease in one patient and in another patient cause was not known. Among women 2 patients had autoimmune hepatitis and one had Wilson's disease. Overall etiology of chronic liver disease could not be found in one patient and reason for acute exacerbation could not be found in 8(17.5%) patients.

Table 12 Etiology of chronic liver disease and reason for acute deterioration

Etiology of CLD (number)	Reason for acute deterioration	Number(percent)
Alcohol (29)	Alcohol HEV unknown	24(82.7) 2(4.4) 3(6.6)
Hepatitis B(9)	Reactivation Alcohol HEV	6(66.6) 2(22.2) 1(11.1)
Autoimmune (2)	Unknown	2 (100)
HCV (2)	Unknown	2(100)
Wilson (2)	DILI Unknown	1(50) 1(50)
Unknown (1)	DILI	1(20)



Mortality and Prognostic factors

13 patients died within 30 days .So 30 day mortality was 29%(13/45) another 5 patient died in the next two months and two patients were referred for transplantation. So the expected 90 day mortality was 44.4 %(20/45). All the patients died due to multi organ failure except two patients who died due intra cerebral hemorrhage. One patient with Wilson's developed intracerebral hemorrhage due to aplastic anemia and severe thrombocytopenia. The cause for aplastic anemia was parvovirus infection. The mean time from hospital admission to death was 22.2 days (3-80). Three (6.6%) patients died within first

week and another 5 patients died (11.1%) in the second week. 8 of the 20 patients (40%) died within the initial two weeks. This shows that initial two weeks is very critical in the management of these patients.One patient with Wilson's disease with super added DILI and another patient with chronic hepatitis B and superadded acute hepatitis E were referred for liver transplantation.

Significant event in patients with ACLF is the development of organ failure. All the patients were admitted with liver failure manifested by coagulopathy. Features of SIRS were present in 34(75%) of patients at admission. Presence of two or more extra hepatic organ failures was considered to be multiorgan failure. 11 (24%) had multi organ failure at admission while another 9(20%) of them developed after admission. Mortality was significantly related to the number of organ failures (Figure.15). Mortality was 7% when there was single organ failure and 33% with two organ failure whereas it was 90% with three organ failure. There was 100% mortality with four or more organ failure.

Patients with hepatic encephalopathy were treated with lactulose and bowel wash. Patients with alcoholic hepatitis were treated with pentoxyfylline and those with reactivation of hepatitis B were given anti virals. SBP was treated with third generation cephalosporin and albumin. Antibiotics used in most

infections were third generation cephalosporin which was changed according to the culture and sensitivity.

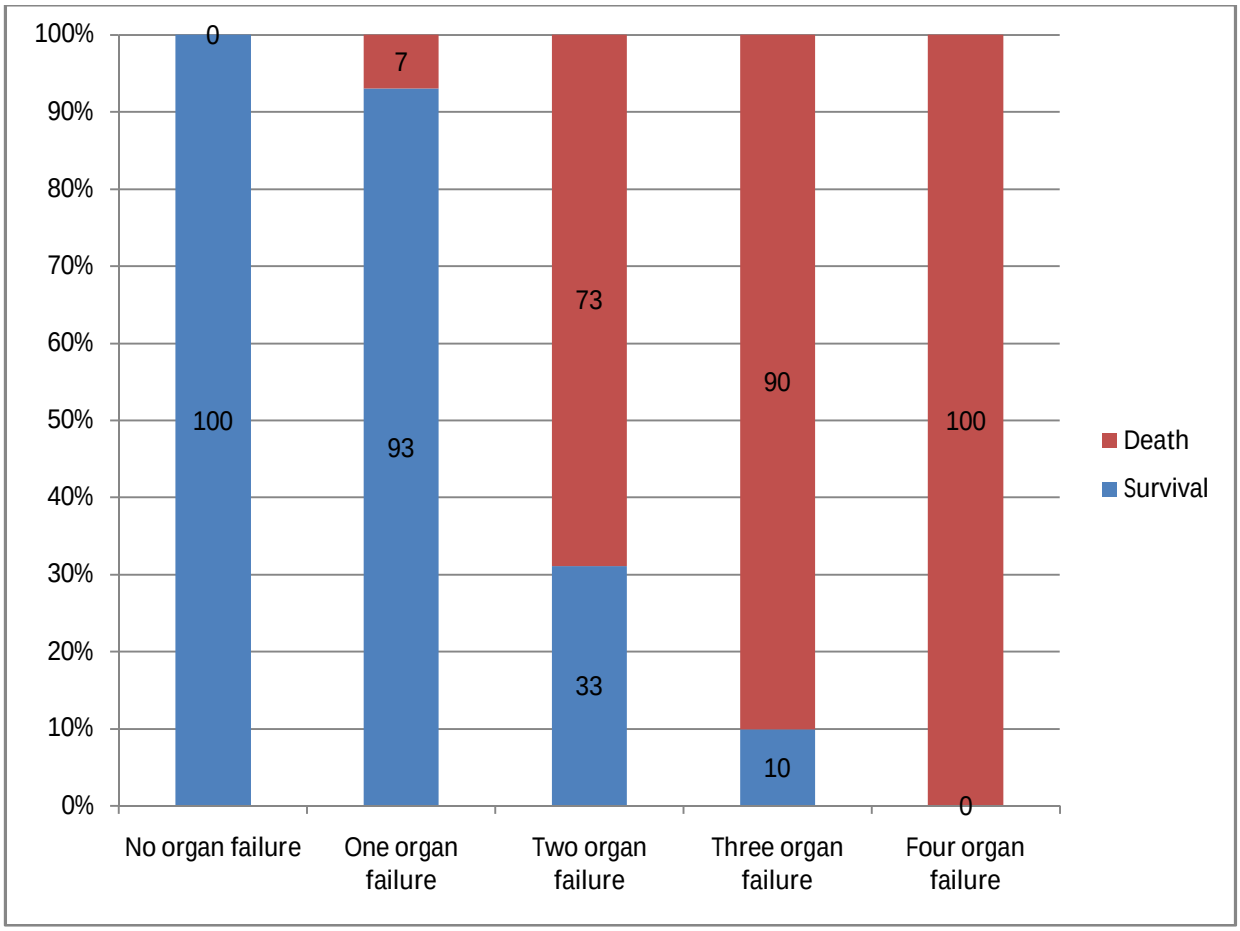


Figure 15 Number of organ failures and mortality

Renal parameters were elevated (creatinine >1 mg/dl) in 17(38%) patients. Causes include prerenal uremia and hepatorenal syndrome. They were treated with fluids albumin and terlipressin. Renal replacement therapy was required

in 15 (33.3%) patients.9 patients were mechanically ventilated for hypoxemia and another 6patients were ventilated for airway protection. Vasopressors were started when mean arterial pressure was less than 65 mm Hg.

All baseline clinical and biochemical parameters were compared to assess the possible predictors of mortality. Survivors had grade 1 or no encephalopathy whereas non survivors had grade 2 or more encephalopathy. Non survivors were found to have elevated WBC count, low platelet count, elevated creatinine, low sodium, higher bilirubin, prolonged PT and INR and higher CRP (table 13). On multivariate analysis platelets, grade 2 or more encephalopathy, high CRP and Meld score were found be significantly associated with mortality.

The ability of various scoring systems like SOFA score, MELD and CTP score was assessed to predict mortality between survivors and nonsurvivors using area under receiver operating curve. AUROC was significantly higher for SOFA and MELD (.897 and .910) score compared to CTP score (.724)

Table 13 Comparison of various laboratory parameters and severity scores in survivors and non survivors

Parameter	Survivors (n=24)	Death or transplantation (n=20)	P value
WBC(cells/cu mm)	12500	17200	0.006
HB (gm./dl)	9	8.60	0.426
Platelets (cell/cu mm)	132000	85000	<0.001
RBS(mg/dl)	101	96.00	0.959
Urea(mg/dl)	28	52.00	<0.001
Creatinine (mg/dl)	.90	1.10	<0.001
Sodium(meq/L)	136	130	<0.001
K+(meq/L)	3.90	3.90	0.603
Bilirubin(mg/dl)	12.00	24.70	<0.001
AST(IU/dl)	135.00	168	0.004
ALT(IU/dl)	95.00	123	0.189
Proteins(g/dl)	5.80	5.50	0.010
albumin(g/dl)	2.90	2.90	0.722
PT(sec)	20.90	26	<0.001
INR	1.74	2.38	<0.001
CRP(mg/dl)	24.00	96	<0.001
MDF	60.35	83.80	<0.001
MELD	23.00	32.00	<0.001
SOFA	4.00	7.00	<0.001
CTP	11.00	12	0.089

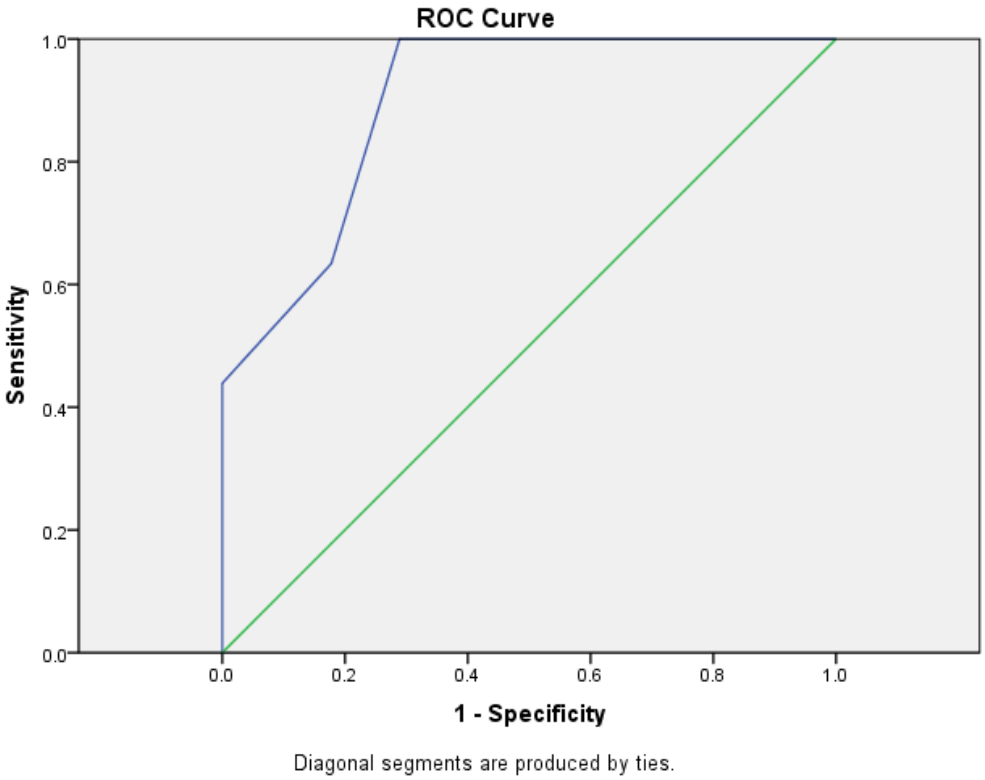


Figure 16 ROC for SOFA score

Area Under the Curve

Test Result Variable(s):SOFA

Area	Std. Error	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.897	.032	.000	.834	.961

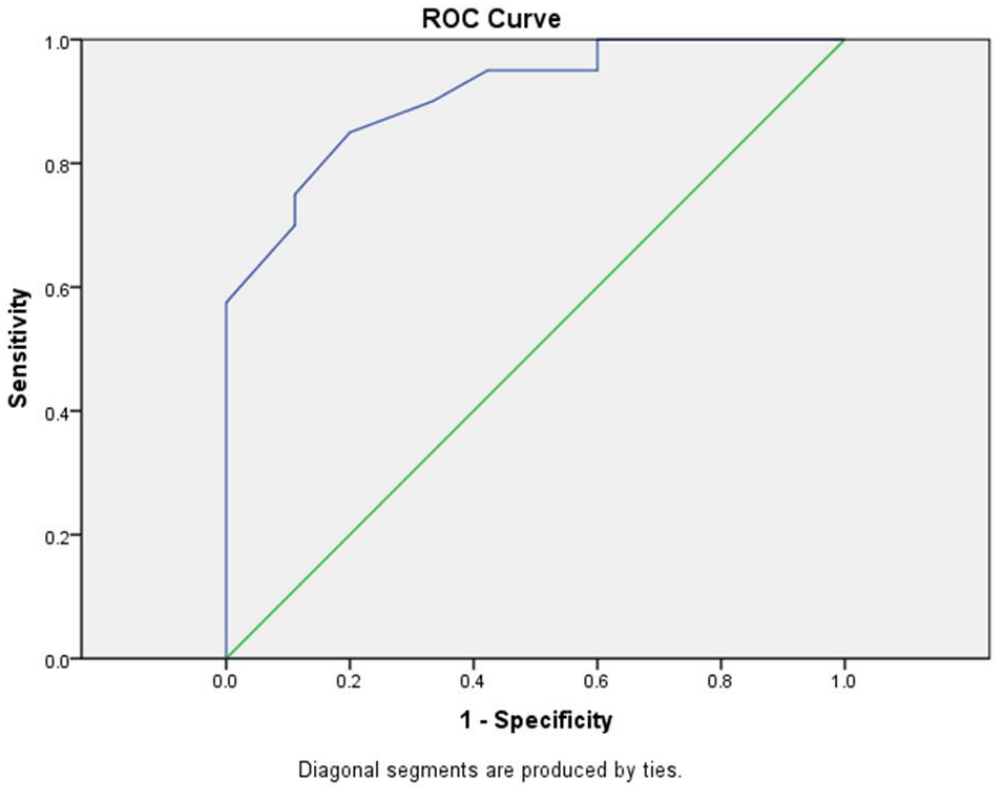


Figure 17 ROC for MELD score

Area Under the Curve

Test Result Variable(s):SOFA

Area	Std. Error	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.897	.032	.000	.834	.961

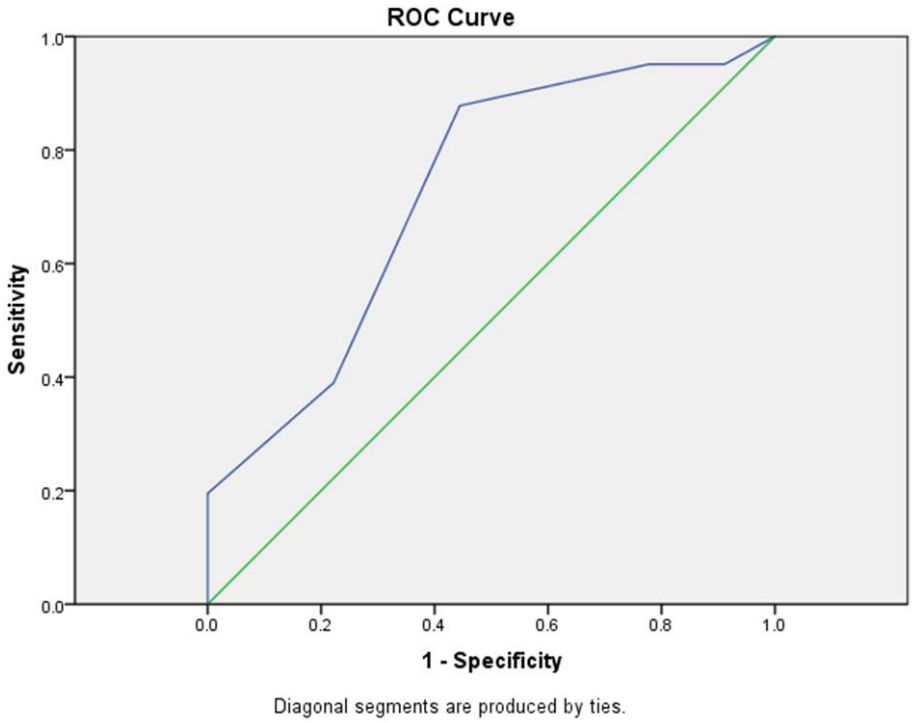


Figure 18 ROC for CTP score

Area Under the Curve

Test Result Variable(s):CTP

Area	Std. Error	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.724	.055	.000	.617	.832

DISCUSSION

DISCUSSION

This is a prospective study which looks into the clinical profile, outcome, precipitating factors and prognostic factors in acute on chronic liver failure. ACLF is a unique entity which defers from chronic decompensation of an end stage liver disease with a rapidly deteriorating presentation and a potential for reversibility. High mortality is mainly due to multiorgan failure. As defined by APASL guidelines all our patients had jaundice and coagulopathy. Jaundice was severe in most patients .Ascites was seen in all patients, but encephalopathy was seen in 63%.Higher grades of encephalopathy was more common in nonsurvivors. About a third of patients had previous history of chronic liver disease.

The most common cause of chronic liver disease in our study is alcoholic liver disease (64.5%). This can be because alcohol is also the commonest cause chronic decompensated liver disease in our department. Most western studies have shown alcohol as the most common etiology followed by viral hepatitis [8, 10]. Patients with alcoholic liver disease are more prone for infection and its complications.It has been observed by Mookerjee et al that these patients have defective neutrophil function and phagocytosis [16]. These neutrophils show increased oxidative burst which means there is a functional failure. In a large prospective study by H Garg et al from Delhi chronic hepatitis B followed

by alcohol and cryptogenic was the common causes [[9]. Duseja et al from Chandigarh found alcohol as the most common insult followed by viral hepatitis and autoimmune hepatitis [41]. Our hospital being a tertiary care center offering a completely free treatment to patients there is a possibility for referral bias in alcoholic being the most common cause.

Alcohol was the most common acute precipitant in alcoholics in our study. Most of our patients have been actively drinking almost till a few days before admission. They were managed by pentoxyfylline in addition to other routine treatment. Hepatitis B reactivation is the most common cause of acute deterioration in chronic hepatitis B. Our findings were similar to findings published in other studies [9, 41] they were started on antivirals.In contrast to other studies acute hepatitis E is the cause of deterioration in only 3(7%) patients. In a study from Acharya et al from Delhi published in 2007 HEV was positive in 50% of patients with acute deterioration[48].Most studies from Indian subcontinent have found acute hepatitis E in 40-60% of patients[49-51]. However these studies cannot be directly compared as the diagnosis of ACLF has not been clearly defined.

In two patients with underlying chronic hepatitis C the reason for acute worsening could not be found out. Transaminases were not elevated and HCV RNA levels low. One patient had severe community acquired pneumonia with

ARDS requiring ventilator support. Another patient had no significant history except for blood transfusion outside prior to admission which was followed by jaundice and ascites.There was no evidence for hemolysis.

One third of our patients had gastrointestinal bleeding, though all had only mild to moderate bleeding. All the patients had bleeding only after the development of jaundice and 5 of them developed after admission only. Most patients had grade 2 varices and portal hypertensive gastropathy. There is a controversy regarding including gastrointestinal bleeding as an acute precipitant [27].In APASL guidelines no consensus has been reached about including gastrointestinal bleeding as an acute event. Based on the observations from our study we can say bleeding was probably due to coagulopathy and stress in most patients and was indicative of sicker patients rather than as trigger for acute deterioration.

Sepsis is important component of ACLF. But whether it is the cause or the result of ACLF is not clear. Patients with chronic liver disease are more prone for infection due increased intestinal permeability leading to bacterial translocation [30]. This bacterial translocation alone is not enough for the rapid downfall. This is combined with defective immune response in the form of abnormal neutrophil function and phagocytosis [8] .Half of our patients had history of fever and almost all the patients had elevated WBC count. Even

though these two features are suggestive of sepsis, infection could be documented in only a third of our patients. Spontaneous bacterial peritonitis is the most common site of infection. Other sites include urinary tract infection, pneumonia, cellulitis and perianal abscess. Most of our patients are referred here after partially treating outside and are invariably on antibiotics by the time they come to us. This could explain the low culture positivity. Other cause of fever in our patients could be alcoholic hepatitis. Most patients had elevated CRP and values were significantly higher in patients who did not survive. So high CRP values especially, persistently elevated values is a poor prognostic marker.

One of the important features of ACLF is the development of organ failure. Presence of two or more extra hepatic organ failures is considered to be multi organ failure. 20 (44%) patients had multi organ failure in our study. 11(24%) had multi organ failure at admission and another 9(20%) of them developed after admission. This shows that once inflammatory cascade sets in it is not always possible to stop it and indicates the severity of underlying disease which leads to progressive organ failure... Mortality was significantly related to number of organ failures. Mortality was significantly related to the number of organ failures. Mortality was 7% when there was single organ failure and 33% with two organ failure whereas it was 90% with three organ failure. There

was 100% mortality with four or more organ failure. So as the number of organ failure increase mortality also increases. This correlation has been shown previously published studies [9, 20]]

Out of 45 patients, 18 patients died in our study and two patients were referred for transplantation bringing the expected mortality to 44.4%. This is similar to mortality in other published studies. However it is lesser than the mortality seen in the study by H Garg.The mean time from hospital admission to death was 22.2 days (3-80). Three (6.6%) patients died within first week and another 5 patients died (11.1%) in the second week. 8 of the 20 patients (40%) died within the initial two weeks. This shows that initial two weeks is very critical in the management of these patients. This importance of initial two weeks has been highlighted in other studies. If the precipitating can be controlled or the organ failures can be prevented in the first two weeks prognosis of the patients can be improved. Two patients were referred for liver transplantation. First patient was having Wilson's disease with drug induced liver injury. She was transplanted seven weeks after admission. Second patient was having chronic hepatitis B with acute hepatitis E. He was transplanted ten weeks after admission. Both of them underwent live donor liver transplant. Both of them are doing well now.

In our study following factors were significantly associated with mortality- lower platelets, presence of renal failure, low serum sodium, high serum bilirubin, prolonged PT, INR and CRP. On multivariate analysis low platelets, Grade 2 or more encephalopathy, MELD score and high CRP were found to be independent predictors of death.

Various prognostic scores have been used to assess the severity of disease in critically ill liver disease patients. It has generally been shown that MELD and SOFA scores are better predictors of mortality than Child score and APACHE score [ ].We have not used APACHE score as it is very cumbersome to use at bedside because of numerous variables and certain parameters like ABG is not always available at bedside. In our study area under ROC is higher for MELD and SOFA than CTP demonstrating that MELD score and SOFA score are more sensitive than CTP score in predicting mortality.

CONCLUSION

CONCLUSION

Acute on chronic liver failure is a unique entity. It is characterized by rapidly deteriorating course in a previously diagnosed or undiagnosed chronic liver disease with a potential for reversibility.

Our study shows that it has high short term mortality (44%). Most common aetiology for underlying chronic liver disease in our centre is alcoholic liver disease (64.5%) followed by hepatitis B (20%) and other causes. The most common acute precipitant is super added alcoholic hepatitis (82%) in alcoholic liver disease and reactivation of hepatitis B (66%) in chronic hepatitis B. Other causes of acute worsening include acute hepatitis E and drug induced liver injury.Most common cause of death is the multi organ failure. Increasing number of organ failures is associated with increasing risk of death. High serum bilirubin, high INR, renal failure,low sodium, and high CRP are all poor prognostic markers. SOFA and MELD are better predictors of mortality than Child score. Early referral for liver transplantation is essential in patients at high risk of death.

Acute on chronic liver failure is a disease which is still being defined and large prospective studies are needed to better delineate the acute precipitants and the prognostic markers.

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ABBREVIATIONS

ACLF	Acute on Chronic Liver Failure
APASL	Asia Pacific Association of Study of Liver
APACHE	Acute Physiology and Chronic Health Assessment
BT	Bacterial Translocation
CRP	C-Reactive Protein
CTP	Child Turcott Pugh
EASL	European Association of Study of Liver
INR	International Normalised Ratio
IL	Interleukin
MDF	Maddrey's Discriminant Function
MELD	Model for End stage Liver Disease
MARS	Molecular Adsorbent Recirculating System
RES	Reticulo Endothelial System
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment

ACUTE ON CHRONIC LIVER FAILURE PROFORMA

Name		IP no		D.O.A	
Age	+	Unit		D.O.Discharge D.O.Death	
Sex		Ward		Duration of stay	
Address			Diagnosis		
Phone No.					
History					
Jaundice			Altered sensorium		
Abdominal Distension			Hematemesis		
Pedal enema			Melena		
Oliguria			Weight loss		
Puffiness of face			Spontaneous bleeding		
Fever			Muscle cramps		
Anorexia			Cough		
fatigue			breathlessness		
Constipation					
Diarrhea					
Native medication					
Past h/o jaundice			Tattooing		
Diabetes			Blood transfusion		
Smoking			Drug abuse		
Alcohol Duration gm/day					

Examination					
HE grade		Clubbing		PR	
Nutrition		Cyanosis		RR	
Height		Parotid swelling		Temp	
Weight		Gynaecomastia		BP Systolic	
BMI		Palmar erythema		Diastolic	
Anaemia		Scrotal swelling		Pulse pressure	
Icterus		Skin changes		Neck veins	
Pedal edema		Abd veins		CVS	
Ascites		Back veins		RS	
Umbilical hernia		Caput medusae			
Splenomegaly		Hepatomegaly			
Investigation					
USG Abdomen Liver Size Echoes Ascites Spleen			Endoscopy		
PV Doppler			CXR		
			CRP		
Ascitic fluid culture Colour SAAG Cell count			PROCALCITONIN		
			Blood culture		
CTP			Urine culture		
MELD		HBsAg		Steroids	
MDF		HCV		pentoxyfylline	
SOFA		Anti HEV		Terlipressin	
HRS		HIV		Albumin	

Date					
TC					
Hb					
Platelet					
RBS					
Urea					
Creatinine					
Sodium					
Potassium					
Bilirubin TOT					
Direct					
Indirect					
SGOT					
SGPT					
ALP					
Protein					
Albumin					
globulin					
PT					
INR					
ABG					
lactate					

Name	age	Sex	A/D	Jaundice	Duration	ascites	encephalopathy	Grade	fever	UGIB	Alc. Use	Hepatomegaly	SPlenomegaly	WBC	HB	Plt	RBS	Urea	Creat	Na	Bili
AM	52	M	A	Y	8	Y	Y	3	N	N	N	N	N	10900	10.4	10000	110	27	1.3	136	5.7
AN	50	M	A	Y	28	Y	N	0	Y	N	Y	N	N	10900	9.5	299000	134	39	0.9	139	21.3
ANDRAI	46	M	A	Y	10	Y	N	0	Y	Y	Y	N	Y	16800	7.7	284000	113	26	0.8	137	9.2
BN	46	M	A	Y	20	Y	Y	3	Y	N	N	N	Y	23000	7.6	85000	121	96	2.1	137	21.7
CS	38	M	A	Y	25	Y	Y	1	Y	N	Y	Y	Y	14300	9.1	87000	82	38	1.1	136	24.9
EI	55	M	A	Y	25	Y	Y	2	N	N	Y	N	N	7000	12.7	100000	40	36	0.7	122	18.9
ER	35	M	A	Y	27	Y	Y	1	Y	Y	Y	Y	N	19200	8.5	78000	96	46	1	134	15.6
GS	42	M	A	Y	20	Y	Y	1	N	N	Y	N	Y	17610	10.1	208000	83	23	0.8	130	12
HI	30	M	A	Y	15	Y	N	0	N	Y	Y	N	N	10600	10.7	147000	103	22	0.7	131	15.5
JPH	42	M	A	Y	28	Y	Y	1	N	N	Y	N	Y	15800	4.3	132000	88	28	0.9	136	24
KN	34	M	A	Y	28	Y	N	0	N	N	Y	Y	N	8100	9	166000	80	20	0.7	136	8.5
KPN	55	M	A	Y	20	Y	N	0	N	N	Y	Y	N	17500	7.4	100000	108	20	0.8	137	8
MI	53	M	A	Y	20	Y	N	0	N	N	N	Y	N	7900	12.7	207000	92	28	1	136	9.7
NA	22	F	A	Y	25	Y	Y	2	Y	N	N	y	y	22,000	8.6	90000	140	38	0.9	134	33
PL	60	M	A	Y	20	Y	Y	0	Y	N	N	N	N	12500	11.2	75000	106	35	0.9	139	15.6
RU	42	M	A	Y	14	7	Y	2	N	Y	Y	N	Y	23,000	5.6	8000	96	64	1.2	137	26.4
RA	32	F	A	Y	22	Y	Y	1	Y	N	Y	N	Y	12300	10.3	140000	98	32	0.9	139	8.2
RMN	70	M	A	Y	15	Y	N	0	N	Y	N	N	Y	9600	6	95,000	76	36	0.9	125	35
RMSH	44	M	A	Y	7	Y	Y	2	Y	N	Y	N	Y	10100	7.3	110000	101	22	0.8	121	5.28
SVN	25	M	A	Y	20	Y	Y	2	Y	Y	Y	N	Y	14100	6.3	102000	62	88	2	131	6.4
SKR	52	M	A	Y	15	Y	Y	2	N	N	Y	N	Y	6200	7.7	141000	141	22	0.7	145	6.3
SLM	35	M	A	Y	15	Y	N	0	N	N	Y	Y	N	11500	8.5	266000	80	20	0.7	145	10.7
SRYA	38	M	A	Y	14	Y	N	0	N	N	Y	Y	Y	12500	8	150000	102	40	1	135	8.2
VKTN	28	M	A	Y	28	Y	N	0	Y	N	Y	Y	Y	26200	10	120000	165	12	0.6	138	15.7
VKTH	36	M	A	Y	28	Y	Y	1	Y	N	Y	Y	Y	14900	9.9	321000	133	75	1.3	134	24.2
AUTN	44	M	D	Y	20	Y	Y	3	Y	N	Y	Y	N	15900	4.6	77000	151	21	0.6	119	11.3
CJVI	46	M	D	Y	25	Y	N	0	N	N	Y	N	Y	12500	11.9	65000	138	41	0.8	126	28.9
KYPN	42	M	D	Y	28	Y	Y	3	N	Y	Y	N	N	19500	7.1	143000	112	48	0.7	129	24.2
KMR	35	M	D	Y	7		Y	2	Y	Y	Y	N	Y	19100	4.3	53000	266	55	1.3	131	5.9
MTI	39	M	D	y	21	y	N	0	y	N	N	N	Y	17200	12.5	272000	95	38	2.9	130	31.9
MHN	42	M	D	Y	28	Y	Y	3	N	N	Y	Y	Y	15100	7.3	164000	72	59	3	125	14.8
NGRJ	30	M	D	Y	10	Y	Y	2	Y	N	N	N	Y	3500	9.3	50000	108	28	0.9	132	26
NSHM	44	M	D	Y	30	Y	Y	3	Y	Y	Y	N	Y	23000	8.4	85000	75	52	1.1	129	33.1
PBU	18	M	D	y	25	y	y	1	N	N	N	N	Y	14500	8.9	46000	104	28	0.9	132	11.6
RJKTH	35	M	D	Y	28	N	N	0	N	Y	Y	N	Y	23900	6.9	70000	69	56	1.4	124	12.7
RMH	40	M	D	Y	28	Y	Y	2	N	N	Y	N	N	17900	8	75000	96	55	1.7	137	24.7
RVI	48	M	D	Y	10	Y	Y	3	Y	Y	Y	N	N	23000	7.5	60000	78	108	4.5	125	23.5
SVRJ	57	M	D	Y	25	Y	Y	3	Y	Y	Y	N	N	19000	12.2	50000	100	199	3.8	136	26.2
SGNM	48	M	D	Y	20	Y	Y	2	Y	N	N	N	Y	580	9.9	55000	75	96	3.4	115	23.5
SVLU	54	M	D	Y	21	Y	Y	3	Y	N	Y	N	y	18700	9.8	250000	142	64	1	125	24
TSM	52	M	D	Y	28	Y	Y	2	Y	N	Y	N	N	9100	9.2	97000	95	24	0.9	130	9.1
VSDN	64	M	D	Y	21	Y	N	0	N	Y	N	Y	Y	12000	9.4	176000	78	45	1	116	38
VLU	45	M	D	Y	14	Y	Y	1	Y	N	N	N	N	9800	7.6	190000	254	128	3.9	130	14.4
SRA	19	F	D/T	Y	20	Y	Y	2	N	N	N	N	y	15600	10.1	125000	110	28	0.9	138	25
SYD	54	M	D/T	Y	25	Y	N	0	N	N	N	N	y	14,500	13	85,000	78	40	1.1	136	26

Name	AST	ALT	TP	Albumin	PT	INR	CRP	Varices	PHG	Sepsis	SBP	Blood Cx	Urine Cx	Other ID	MDF	CTP	MELD	SIRS	SOFA	DIALYSIS	MOF AT ADM
AM	256	296	6	3.1	19	1.7	24	2	Y		N					11	21	Y	7	N	N
AN	135	75	5.7	3.2	23	1.9	48	2	N		N				67.3	12	25	Y	4	N	N
ANDRAI	135	95	5.9	2.9	22	1.7	6	0	N		N				50.6	11	21	Y	3	N	N
BN	197	220	5.4	2.6	29	2.9	48	2	Y	y	N			CELLULITIS		14	37	Y	6	Y	Y
CS	156	85	5.8	3.2	20.9	1.6	96	2	Y	y	N	KLEBSIELLA			66	10	25	Y	7	N	N
EI	126	112	5.4	2.2	20	1.7	6	2	n		n				51.1	13	26	N	5	N	N
ER	134	120	5.2	2.4	23	1.8	96	1	Y	y	Y				66.2	11	23	Y	7	N	N
GS	72	24	6	1.9	19	1.5	24	2	Y	y	N			PERI ANALABCESS	44.2	12	20	Y	5	N	N
HI	98	196	5	2.7	20.9	1.74	24	1	Y		N				66.1	11	23	N	4	N	N
JPH	56	39	6.6	3.7	20.3	1.94	24	2	Y		N				43	11	24	Y	5	N	N
KN	124	188	5.4	2.9	23.9	2.22	48	2	Y		N				59.1	12	23	N	3	N	N
KPN	148	76	6.2	3.4	20.2	1.56	24	2	N		N				40.2	9	19	N	3	N	N
MI	192	151	6.5	3.8	19	1.5	24	1	N		N					9	20	N	3	N	N
NA	247	346	5.4	2.6	25	2.6	96	2	0		N					11	30	Y	6	N	N
PL	196	235	5.8	2.9	20	1.8	24	2	N		N					10	23	N	4	N	N
RU	148	96	5.3	2.6	26	2.7	96	2	Y		N				90.4	12	32	Y	10	Y	Y
RA	80	75	5.9	2.9	20	1.7	24	1	N		N				40.4	12	20	Y	6	N	N
RMN	45	35	5.2	2.5	25	2.3	48	4	Y		N					13	29	N	6	N	N
RMSH	78	62	5.1	1.8	26.8	2.08	48	2	Y	y	n		KLEBSIELLA		69.7	13	21	Y	3	N	N
SVN	135	92	6.1	3.3	25	2.2	6	2	Y	y	N			CELLULITIS	61.6	13	29	Y	7	N	N
SKR	170	230	6.3	3.4	17	1.5	46	2	N		N					11	18	N	4	N	N
SLM	78	134	5.8	2.6	20	1.6	6	0	N		N					11	21	N	3	N	N
SRYA	170	132	5.8	0	26	2.2	24	3	N		N				67	10	24	N	4	N	N
VKTN	137	61	6.6	2.5	26.5	2.16	24	2	Y		N				77.8	12	25	Y	4	N	N
VKTH	75	38	5.4	2.3	19	1.5	24	2	N	y	Y				51.8	13	26	Y	5	N	N
AUTN	138	123	3.6	1.9	25.9	2.01	96	1	N		N				74	13	24	Y	8	N	N
CJVI	100	62	5.2	3	23	1.78	94	2	Y		N				75	11	26	Y	6	N	N
KYPN	143	73	6.6	3.5	29	2.7	24	2	Y		N				102	12	39	y	7	y	N
KMR	56	42	6	3.1	31.5	2.38	96		Y		N				93.3	12	25	Y	7	Y	N
MTI	249	118	6	2.3	22.3	1.91	96	2	y		n				78	12	37	y	6	y	y
MHN	115	125	6	3.2	26.9	2.22	96	2	Y	y	n		KLEBSIELLA		83.8	12	36	Y	6	Y	N
NGRJ	250	225	5	2.9	42.5	4.02	96	2	Y	y	Y	PSEUDOMONAS				13	34	Y	9	N	Y
NSHM	171	66	5.2	3.1	20	1.9	96	2	y	y	N	CONG			86	14	27	Y	8	Y	N
PBU	237	298	5.3	2.8	24	2	48	0	N		N					11	23	N	4	N	N
RJKTH	95	82	5.2	2.6	34	2.9	48	1	Y	y	Y	KLEBSIELLA			113	12	31	Y	9	Y	Y
RMH	104	51	5.5	3.1	19	1.5	98		Y		N				52.3	12		Y	8	Y	N
RVI	128	147	5.3	2.3	45	4.5	96		Y	y	Y	KLEBSIELLA			123	14	48	Y	14	Y	Y
SVRJ	310	1642	5.2	3	23	1.9	96	3	N		N				77	12	39	Y	13	Y	Y
SGNM	168	190	5.7	2.8	36	3.5	96	2	Y		N				128	14	44	Y	7	Y	Y
SVLU	104	37	5.6	2.2	24	2	238	2	Y	y	N			PNEUMONIA	75.2	14	26	Y	9	N	y
TSM	186	121	6	3.9	24	1.9	24	3	Y		N				64.3	12	22	Y	6	Y	N
VSDN	256	240	5.3	2.9	38	3.86	96	3	Y		N					13	35	Y	6	Y	N
VLU	58	80	5.6	2.6	24	2	96	0	N	y	N			PNEUMONIA		9	37	Y	7	Y	Y
SRA	250	200	5.5	2.9	27	2.5	96	2	N		N					13	29	Y	6	N	n
SYD	350	458	5.5	3	28	3	96	2	N		N					12	29	Y	6	N	Y

Name	MOF aft adm	Etiology	acute cause	No of organ failure	PAST H/O CLD	CAUSE OF DEATH
AM	N	HEP B	HEP B	1	N	
AN	N	ALCOHOL	ALCOHOL	1	N	
ANDRAI	N	ALCOHOL	ALCOHOL	1	N	
BN	y	HEP B	HEP B	3	Y	
CS	N	ALCOHOL	ALCOHOL	1	N	
EI	N	ALCOHOL	ALCOHOL	1	N	
ER	N	ALCOHOL	ALCOHOL	1	Y	
GS	N	ALCOHOL	ALCOHOL	1	N	
HI	N	ALCOHOL	ALCOHOL	1	N	
JPH	N	ALCOHOL	ALCOHOL	1	N	
KN	N	ALCOHOL	ALCOHOL	0	N	
KPN	N	ALCOHOL	ALCOHOL	0	N	
MI	N	HEP B	HEP B	0	N	
NA	N	AUTOIMMUNE	CRYPTO	2	Y	
PL	N	CRYPTO	DILI	1	N	
RU	Y	ALCOHOL	ALCOHOL	2	N	
RA	N	AUTOIMMUNE	CRYPTO	0	N	
RMN	N	HCV	CRYPTO	1	Y	
RMSH	N	ALCOHOL	ALCOHOL	0	N	
SVN	N	ALCOHOL	CRYPTO	1	Y	
SKR	N	HEP B	HEP B	0	Y	
SLM	N	ALCOHOL	ALCOHOL	0	N	
SRYA	N	ALCOHOL	HEV	0	N	
VKTN	N	HEP B	ALCOHOL	1	N	
VKTH	N	ALCOHOL	ALCOHOL	1	N	
AUTN	Y	ALCOHOL	ALCOHOL	3	Y	MOF
CJVI	Y	ALCOHOL	ALCOHOL	3	N	ICH
KYPN	Y	ALCOHOL	ALCOHOL	4	N	MOF
KMR	N	ALCOHOL	ALCOHOL	3	N	MOF
MTI	y	ALCOHOL	ALCOHOL	4	Y	MOF
MHN	Y	ALCOHOL	ALCOHOL	3	N	MOF
NGRJ	Y	HEP B	HEP B	3	Y	MOF
NSHM	Y	ALCOHOL	ALCOHOL	6	N	MOF
PBU	N	WILSON	CRYPTO	1	Y	ICH
RJKTH	Y	ALCOHOL	ALCOHOL	3	N	MOF
RMH	Y	ALCOHOL	ALCOHOL	3	Y	MOF
RVI	Y	ALCOHOL	ALCOHOL	2	N	MOF
SVRJ	Y	ALCOHOL	HEV	4	N	MOF
SGNM	Y	ALCOHOL	CRYPTO	4	N	MOF
SVLU	Y	Hep B	alcohol	4	N	MOF
TSM	Y	ALCOHOL	CRYPTO	3	Y	MOF
VSDN	Y	HEP B	HEP B	3	Y	MOF
VLU	Y	HCV	CRYPTO	2	N	MOF
SRA	Y	WILSON	DILI	2	N	MOF
SYD	y	Hep B	HEV	2	Y	MOF

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Hemamala VS
PG in Medical Gastroenterology
Madras Medical College, Chennai -3

Dear Dr.Hemamala VS

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Acute on chronic liver failure – Clinical profile, precipitating factors, outcome and predictors of mortality" No.22042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3.	Prof. B. Kalaiselvi MD Prof. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md. Ali. MD.DM Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof.P.Karkuzhali MD Director i/c, Prof., Inst. of Pathology MMC, Ch-3	-- Member
7.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
8.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

INFORMATION SHEET

- We are conducting a study on **"Acute on Chronic Liver Failure – Clinical profile precipitating factors, mortality and predictors of outcome"** at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003.

- The purpose of the study is
  - to study the clinical features, precipitating factors, mortality and predictors of outcome in patients with acute on chronic Liver failure.

- At the time of announcing results and suggestions name and identity of the patients will be confidential.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator ***Signature of Participant***

Signature of the Relative/Guardian

PATIENT CONSENT FORM

Study details: A study on "**Acute on Chronic Liver Failure – Clinical profile precipitating factors, mortality and predictors of outcome"**

Study Centre: Rajiv Gandhi Government General Hospital,
Madras Medical College, Chennai-600 003.

Patient may check (☑) these boxes

I confirm that I have read and understood the Information Sheet for the above study. I have- had the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I understand that the Clinical study personnel, the Ethics Committee and the Regulatory Authorities will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study. ☐

Signature / Thumb Impression: _____ Place Date
of the patient

Patient's Name, Address & Ph No: _____

Name of the Investigators : _____

Signature of the Investigator: _____ Place_____ Date

Institution: _____

Signature of the Relative/Guardian: _____

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் நோயாளிகளில், கல்லீரல் நோயினால் பாதிக்கப்பட்டவர்கள் குறித்த ஆய்வு இங்கு நடைபெற்று வருகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களை பங்கேற்க வைத்து அதன் தகவல்களை ஆராய்வோம். அதனால், தங்களின் நோயின் ஆய்வறிக்கையோ, சிகிச்சையோ பாதிக்கப்படாது என்பதைத் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம்

பங்கேற்பாளரின் உறவினர் கையொப்பம்

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

"கல்லீரல் நோயினால் பாதிக்கப்பட்டவர்களைப் பற்றிய ஆய்வு"

ஆராய்ச்சி நிலையம் : இராஜீவ்காந்தி அரசு பொது மருத்துவமனை
சென்னை மருத்துவக்கல்லூரி,
சென்னை - 600 003.

பங்கு பெறுபவரின் பெயர் :

பங்குபெறுபவரின் எண் :

பங்கு பெறுவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தகமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், ஊடுகதிர் படம் மற்றும் மின் உடலியங்கியல் பரிசோதனை செய்துகொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

நோயாளியின் உறவினர்/காப்பாளர் கையொப்பம் ..... இடம் ..... தேதி

ACUTE ON CHRONIC LIVER FAILURE-CLINICAL PROFILE, PRECIPITATING FACTORS, OUTCOME AND PREDICTORS OF MORTALITY

Dissertation submitted in partial fulfillment of requirements for

DM DEGREE IN MEDICAL GASTROENTEROLOGY

BRANCH IV

of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,
CHENNAI, INDIA.

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ACUTE ON CHRONIC LIVER FAILURE-CLINICAL PROFILE, PRECIPITATING FACTORS, OUTCOME AND PREDICTORS OF MORTALITY Dissertation submitted in partial fulfillment of requirements for DM DEGREE IN MEDICAL GASTROENTEROLOGY BRANCH IV of THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, INDIA. MADRAS MEDICAL COLLEGE, CHENNAI 600003 AUGUST 2013 INTRODUCTION Liver failure can develop acutely in a patient with no preexisting liver disease (acute liver failure) or as an acute decompensation of a chronic liver disease. Recently it has been noted that a subgroup of patients develop acute deterioration in previously compensated cirrhosis and are considered to have acute on chronic liver failure(ACLF). This...